BRAIN.

PART 3, VOL. 49.

IDIOPATHIC NARCOLEPSY: A DISEASE *SUI GENERIS*; WITH REMARKS ON THE MECHANISM OF SLEEP.

BY W. J. ADIE, M.D., F.R.C.P.

Physician to Out-patients, the National Hospital, Queen Square, London.

(From a Thesis submitted for the Degree of M.D. in the University of Edinburgh, on February 26, 1926.)

	PAGE
1.—INTRODUCTION	257
2.—DESCRIPTION OF CASES	259
3.—GENERAL DESCRIPTION OF THE DISEASE—	
(*a*) Ætiology	267
(*b*) The Attacks	269
4.—THE NATURE OF THE ATTACKS	275
5.—DIAGNOSIS	279
6.—THEORETICAL CONSIDERATIONS—	
(*a*) Narcolepsy and Pavlov's Researches on Sleep	283
(*b*) Symptoms of True Narcolepsy after Encephalitis Lethargica	291
(*c*) Narcolepsy and the Pituitary 'Tween-Brain System	293
(*d*) Narcolepsy and Subcortical Sleep Centres	298
7.—SUMMARY—	
(*a*) The Facts	303
(*b*) Conclusions	304

INTRODUCTION.

THE disease I am about to describe is characterized by the occurrence of attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly, so that the victim sinks to the ground fully conscious but unable to move. As a rule the attacks occur independently; occasionally an attack on emotion ends in sleep.

The first case was described by Westphal [37] in 1887 in a paper on "eigenartige mit Einschlafen verbundene Anfälle"; in the following year Fischer [4] reported a similar case; in 1880 Gelineau [6] described another and used the name narcolepsy for the first time. Both Westphal

and Fischer applied the term epileptoid to the attacks, but Gelineau asserted that he had described "a new species of neurosis" that had nothing to do with epilepsy whatsoever.

Thanks to the writings of Henneberg [9], Goldflam [7], Redlich [23] and others, the disease is well known in Germany. In other countries the word "narcolepsy" is applied indiscriminately to untimely or excessive sleep in epilepsy, hysteria, pituitary disease, cerebral tumour and other nervous and general disorders, whereas true narcolepsy is mistaken for epilepsy or hysteria. One of my objects here is to rescue the word narcolepsy from the confusion that now surrounds it, and to reinstate it as the name of a highly remarkable and by no means very rare disease, with peculiar and unmistakable features that distinguish it clearly from epilepsy and all other morbid conditions in which excessive or untimely sleep is an occasional symptom.

I shall base my description of the disease upon an analysis of six cases that have come under my own observation and fifteen recorded in journals available in the library of the Royal Society of Medicine. I have not included all the published cases—they number about forty in all—but those I have chosen as examples of true narcolepsy, together with my own cases, will suffice, I think, to prove that the peculiar combination of symptoms in this disease recurs with a frequency and uniformity that justify its description as a distinct disease. In these matters, "The right question is," as the late Sir Clifford Allbutt wrote, "Have I noted in a moving equilibrium, say in man, that a certain series of changes, static and dynamic, has occurred more than once? If so, was the recurrence still fortuitous, or was the series a case of an orderly recurrent mode, which hitherto had escaped attention? If so, the recurrence will be observed again and again by myself or by others in approximate uniformity. The cases of the newly observed series will vary, some indeed so far as to trespass upon other nosological series already recognized, and no strict demarcation can be drawn around them; yet there may, nevertheless, be difference enough and constancy enough to make it worth our while, for the convenience of observation and thought, to erect the new series into a category of its own, and to stick a label on it."

In the case of narcolepsy the answer to this question must be "yes." The "new series" *is* worthy of a label because, for one reason, it comprises cases that are at present confused with the "orderly recurrent mode" we call epilepsy, and it is certainly convenient "for observation and thought," and highly important for our

patients, that we should distinguish it from a serious disease with which it has no connection whatever.

After describing the cases briefly I shall analyse them and consider the differences between narcolepsy and certain other diseases. I shall then discuss the symptoms and attempt to explain their nature. This will entail a short inquiry into the mechanism of normal sleep and a brief review of Pavlov's researches on internal inhibition and sleep. I shall attempt to prove that the two "kinds" of attack in narcolepsy are essentially the same, and not different in kind as has hitherto been thought. Further, I hope to support Pavlov's conception that "internal inhibition and sleep are one and the same process"—a conception based upon the results of experiments on dogs, with evidence gained from the study of narcolepsy, a disease of man.

Finally, I shall attempt to reconcile prevailing notions of the mechanism of sleep, based on the assumption of "sleep centres" in subcortical centres, with Pavlov's work which seems to prove that normal sleep is a function of the cerebral cortex.

Description of Cases.

Case 1.—Olive P., aged 14, came to the National Hospital, Queen Square, as an out-patient in September, 1923; her complaint was that "she has attacks in which she comes over faint and falls" (? transient loss of consciousness); a diagnosis of *petit mal* was made and bromide and luminal were ordered; these had no effect upon the attacks. I saw her for the first time in May, 1924, and have seen her at regular intervals since. At her first visit I wrote down her own words: "When I laugh I cannot stand; I must sit down in a chair or I will fall." Thinking her case was one of *Lachschlag* (Oppenheim) I looked up this subject and came across Gelineau's description of narcolepsy. At her next visit I questioned her closely and obtained the following information: She suffers from two kinds of attack; in some she sleeps, in others she falls on laughing heartily. She has always been a heavy sleeper and is always rather sleepy during the day; during her twelfth year she began to sleep in spite of efforts to remain awake, and since then she has slept several times every day; this is most likely to happen when she sits in a chair with nothing to occupy her attention, but she has often slept while riding in public vehicles, when walking in crowded streets and at other inconvenient times. When the inclination to sleep is felt she must sleep, however hard she tries to prevent it; she appears to be in ordinary quiet sleep; if she is not disturbed she sleeps for five or ten minutes; she is easily wakened by a call or a light touch; she is wide awake at once and knows that she has slept; although she cannot resist sleep a sharp word or a shake from her mother dispels the feeling of sleepiness at once and prevents the attack.

The other attacks are usually brought on by laughing: "If anybody makes me laugh I fall down," "If anyone tells me a joke and I see it very much my eyes go misty, I feel funny in the head, and if I don't sit down I fall down." In these attacks "she opens her mouth, her head falls forward, the arms fall to her side and the knees give way; she does not lose consciousness but is unable to move or speak; it lasts about half a minute; she never sleeps in these attacks." Anger and annoyance produce the same symptoms in a lesser degree.

I have questioned the patient and her mother very closely on many occasions but have never obtained an account of anything resembling an epileptic attack. The family history is good; no member as far as is known has suffered from epilepsy or any mental disease; she has six healthy brothers and sisters; her previous health has been remarkably good; apart from measles and chicken-pox she has never suffered from any illness; she did well at school. She is a well-developed, healthy-looking child; the menses began at the age of 13; they are not yet regular; a careful physical examination reveals no evidence of disease. She is quiet in her manner and rather shy, but on longer acquaintance she became less reticent and discussed her symptoms freely; her intelligence is normal and she is well informed for her age. I have conversed with her and her mother on about twenty occasions, and have formed the impression that apart from the attacks she is a perfectly normal girl physically and mentally.

The sleep attacks have not altered in frequency during the year that she has attended the hospital. She has now learned to check herself when she feels inclined to laugh, and the falling attacks are therefore not so frequent as before. I have not seen her in a sleeping attack and I was unable to provoke an attack on laughing.

Case 2.—Freda W., aged 19, was admitted to the National Hospital, Queen Square, under the care of Dr. James Taylor, in 1923. She complained of falling asleep at her work and of falling down when she laughed. Apart from childish complaints her general health was good; the menses appeared at the age of 15; during her seventeenth year they were irregular but they are now normal; her father, mother, brother and sister are all alive and well; one brother was killed in action; there is no history of nervous or mental trouble in the family.

During the summer of 1918, when she was 14 years old, she began to sleep at odd times during the day, at meals, working in the house, walking in the street and when riding a bicycle; on one occaion she fell into the fire and burnt her wrists; on another she fell from her bicycle and slept in the middle of the road. She is quite unable to resist sleep; she feels drowsy, her head feels "as if the brain wants to expand" and in a few moments she is asleep; she wakes easily if touched or called and then feels as if she had been asleep in a stuffy room. Under observation in hospital she had about ten attacks of sleep each day; her appearance during the attack was that of a person in normal, quiet sleep.

About a year after the sleepiness appeared she noticed that if she laughed heartily the "limbs crumpled up" and she fell down; such an attack very often ended in a short sleep. At first she always slept for a time after falling down through laughing, but now these attacks are sometimes slighter, so that although she falls she remains quite conscious of her surroundings. One of these attacks was observed while she was in hospital: after laughing the lips and eyelids trembled, the head fell, she lay back on the pillow and slept for about thirty seconds.

A complete physical examination revealed nothing abnormal except that the pituitary fossa was small. Memory and intelligence were normal. She slept well at night. The attacks became much less frequent while she was resting in hospital, but she reported that they became more frequent again when she returned to her work as a domestic servant.

Case 3.—Mrs. C., aged 42, complained of attacks from which she had suffered for several years: the first attack occurred when she heard that a boy who was cycling from London to spend a week-end at her home had been killed on the way; on hearing this news "all the power went from me" and she sank upon a couch, where she lay powerless, unable to move and unable to say a word: since then she has had many attacks, sometimes after laughing heartily but more often after some unpleasant emotion. These attacks cause her great distress, and she now has a morbid fear that she will be found in an attack and looked upon as dead. Her eyes close at the onset of the attack and she is forced to lie down: she tries to cry for help but no sound is emitted and she makes no movement: she hears and understands everything that goes on around her and is greatly distressed because she cannot answer sympathetic inquiries. She has never fallen asleep after one of these attacks, but she has always been a "sleepy-head" and has often dropped off to sleep at inappropriate times; when the inclination to sleep is felt, nothing she can do prevents it. She consulted several physicians who diagnosed hysteria; a London consultant said she had "epilepsy without convulsions" and ordered anti-epileptic remedies. Her physical condition is good, and there is nothing in her personal or family history to account for the attacks.

Case 4.—Captain X., aged 35. This officer spoke to me after a lecture and apologized for falling asleep, saying that it was impossible for him to keep awake when his attacks came on. He has had the attacks since the age of 20; he sleeps many times every day under all conceivable circumstances; on one occasion he fell asleep while driving his car. I sat near him on a guest night at his Corps' Mess and noticed that he fell asleep twice during dinner. He served throughout the war, but noise, danger, and excitement did not prevent the attacks. If he laughs heartily he goes "floppy all over" and must support himself or sit down. He comes of a healthy family and is himself perfectly healthy in every other respect. It did not occur to him that he was suffering from any definite disease and he has never sought medical advice for his

troubles, although his comrades never allow him to forget that he is different from normal individuals.

Case 5.—Gelineau [6]. A cooper, aged 38; good family and personal history. For two years he has had attacks in which he loses the use of his legs, which give way beneath him; these attacks come on when he laughs heartily or has any pleasurable emotion such as the prospect of a good business deal, or when he holds a good hand at cards. He is worried at all times by an inclination to sleep, and the attacks of weakness on emotion often end in his falling asleep for a few moments; during a meal he may fall asleep four or five times; his knife and fork fall, the sentence he began in a loud voice ends feebly, his head sinks and he sleeps for a few seconds or minutes; he tries to prevent this by rubbing his eyes but his hand falls powerless; the only way to waken him is to shake him violently; on waking his head is clear and he feels quite fresh; he has innumerable attacks in the course of a day. In other respects he is perfectly healthy; his memory and intelligence are intact.

Case 6.—Löwenfeld [14]. Male, aged 17½. Diphtheria aged 6; no other illnesses; parents and four brothers and sisters healthy; an aunt paranoiac. He was one of the best scholars in his class throughout his school life, but from the age of 13½ progress was impeded by attacks in which he went to sleep; at first they occurred in the afternoons only, but now they come on at any time, sometimes with only ten or fifteen minutes' interval; at first they lasted for a few seconds only, but now they last several minutes or longer. He passed through the Realschule and works regularly in a factory. He gets no warning of the attack; it may come on under any circumstances, e.g., at meals, at work, or when walking home after his work; he wakes up when he strikes some object or a passer-by, or when he steps off the kerb; he is in full possession of his senses at once; the attacks which were observed resembled normal sleep. When he laughs his muscles relax, objects fall from his hands, his jaw falls and he is unable to close his mouth. On examination he appeared to be in perfect physical and mental health.

Case 7.—Stöcker [34]. Male, aged 15; no serious illnesses, good family history, was always the best scholar in his class in the village school. For six months has had three or four attacks of sleep each day, lasting ten to thirty minutes; at work he can sometimes delay sleep until he has finished a particular task, but he must sleep sooner or later; he has slept sitting and standing in vehicles and passed his destination, at meals when he drops his knife and fork, and walking in the street when he wakes on bumping into something; he is easily wakened by a call and is wide awake at once; in the attacks he appeared to be sleeping normally. If he is suddenly called upon to do a difficult piece of work he has a feeling of general weakness; when larking with his mates his strength suddenly goes and the weakest can do what he will with him. His night sleep is normal. Physically and mentally he appears to be in perfect health.

Case 8.—Redlich [25]. Male, aged 19; no serious illnesses; father alcoholic, family history otherwise good; did moderately well at school. For six months has had two or three attacks a day in which he falls asleep for five or ten minutes; if he lies down he sleeps longer; he once slept for twelve hours. He can resist the desire to sleep for some time but cannot prevent it altogether, and the more he resists the longer he sleeps; the attacks generally come on at 10 a.m., during the midday rest, and at 4 p.m.; in the intervals he is tired and sleepy, and yawns frequently; he is easily wakened. For four months he has noticed that if he laughs heartily he has a feeling that he is going to fall, the knees give way and he lets things fall from his hands. He is perfectly healthy in every other respect.

Case 9.—Henneberg [9]. Male, aged 26; father has tabes, a brother disseminated sclerosis; enuresis till the age of 6; rheumatic fever, aged 6; chorea, aged 8 and 13; works as a cooper; is a gymnast and cyclist.

For five years has fallen asleep five or six times a day for about fifteen minutes; the attack begins with a feeling of overwhelming fatigue, the lids feel heavy, and although he can sometimes resist the inclination to sleep for half an hour or so it is inevitable; he sleeps when playing cards, eating, smoking, reading and when riding his bicycle; he very seldom falls because he has time to get off his bicycle and lean against a wall. He once slept on listening-post duty in the trenches although his tour lasted half an hour only and he was well aware of the penalty; he is easily wakened and feels fresh at once; between the attacks he feels well and is not tired or sleepy.

If he laughs heartily his head falls forward, the jaw falls and the knees give way; he does not fall and is fully conscious during the attack; anger rarely causes these attacks, but on one occasion when about to chastise his child his arm fell powerless to his side and his knees gave way beneath him. Examination revealed no mental or physical disease.

Case 10.—Jolly [11]. Male, aged 36; good family history; frequent nose-bleeding; rather backward at school; drank heavily for a few years; no serious illnesses. Six years ago, after a period of great exertion with little sleep, he began to fall asleep and had to be taken away from machinery. He usually sleeps if he sits down for more than a few minutes, especially if the weather is warm; he sometimes sleeps when walking in the street, and once was nearly struck by a passing tramcar. If he laughs heartily or feels any strong emotion the head falls forwards, the jaw drops, the knees give way and he sinks to the ground unable to move for a minute or so; he is wide awake during these attacks. Otherwise he is healthy.

Case 11.—Mendel [16]. Male, aged 26; good family history; nose-bleeding almost daily from the age of 8 to 22, none since. Always feels tired and sleepy; for four years he has fallen off to sleep several times a day for about fifteen minutes; he is most likely to go off in a warm room, in dull weather or after the midday meal, but he has slept in the middle of an inter-

esting conversation, whilst reading a newspaper, during meals, during a heavy bombardment and on the march; he once fell asleep on listening-post duty in the trenches and narrowly avoided the penalty for this offence. He can laugh heartily with impunity, but if he feels angry his knees give way, his head falls forward and he feels quite helpless. He is healthy in other respects.

Case 12.—Singer [30]. Male, aged 33; good family history; previous health good. For fifteen years has fallen asleep two or three times a day for about fifteen minutes; the attacks are preceded by a feeling of intense fatigue; he can sometimes resist sleep for a time, but if successful he sleeps longer in the end; the attacks may come on at any time, e.g., during meals, on a bicycle or on horseback, ploughing, dancing, singing in church, in the ranks on the march, at his post in the trenches and during coitus; he is easily awakened, remembers the attack and aura and feels fresh at once. If he laughs heartily or is annoyed he grimaces and his knees give way but he does not fall.

Case 13.—Stiefler [32]. Male, aged 31; Bell's palsy at the age of 18, otherwise always healthy; drank alcohol to excess between the ages of 18 and 26, teetotal since. His father, mother and three brothers were all alcoholic; apart from this the family history is good. He has one healthy child, none dead. He did well at school but was often reproved for inattention because he fell asleep; later he was discharged several times by various employers for the same reason.

He now has attacks in which he falls asleep, about four or five every day; they last several minutes as a rule, but longer when the circumstances are favourable; he once slept from mid-day well into the night. The attacks are preceded by a feeling of intense fatigue and sleep cannot be prevented. They are more likely to come on during vigorous exercises than at other times; he has had them in the most diverse circumstances, even when standing or walking in busy streets; he bears two scars on his forehead caused by bumping into lamp posts. On waking he feels quite fresh, knows he has slept and can sometimes remember dreams. Several attacks were observed; they resembled normal light sleep; he roused at once in response to a call or a shake. Laughter caused no trouble, but anger and annoyance caused a sudden feeling of helplessness, his legs gave way and he was unable to speak; he retained full consciousness during these attacks. Between the attacks he has a constant slight feeling of sleepiness. His night sleep is sound and prolonged. On examination his physical and mental condition was normal.

Case 14.—Noack [18]. Male, aged 33; good family history, no other illnesses. Has had sleep attacks for six years, about six a day, lasting five to forty minutes; he once slept from Saturday night till Monday morning; he can ward off an attack for a time by walking briskly, but always sleeps in the end; sleep comes on when he is sitting in vehicles, at meals, at work, when smoking or when walking in the street. When he laughs or is angry his head falls to one side as if loose, the arms hang loosely, he drops things from his

hands and the legs give way. He is slightly feeble-minded and always feels tired and sleepy.

Case 15.—Somer [31]. Male (age at time of observation, family and personal history and duration of symptoms not given).

Falls asleep "frequently" under all circumstances, especially after meals: hears what is going on around him and tries to speak, but makes irrelevant remarks—this annoys him and wakens him; he sleeps sometimes while walking on the road and is wakened by striking something or stumbling. He had several attacks while under observation with every appearance of normal sleep, from which he was easily awakened by shaking. He also has attacks on emotion, e.g., when laughing heartily, when about to strike his child, or whilst considering a difficult stroke at billiards; in these attacks the head falls, the lids droop, the limbs relax, he sinks slowly to the ground and is unable to move for half a minute; he remembers everything he hears during these attacks.

Case 16.—Somer [31]. Male, aged 20; good family history; no serious illnesses; blow on head, aged 8, not severe. Duration of symptoms not given; admitted for sudden attacks of weakness, which caused him to sink slowly to the ground quite conscious but unable to move for a minute or so; these attacks are brought on by hearty laughter and other emotional disturbances. An attack was observed while he was dressing; his head sank, his knees gave way, he slipped down and remained sitting for half a minute; when ordered to speak he stammered, then opened his eyes slowly, spoke clearly, stood up, and finished dressing himself. In some attacks he was able to repeat what was said to him, he remembers everything that happens during the attack. One day he was found fast asleep; he stated that he often fell asleep in the daytime. Physical and psychological examination revealed nothing abnormal.

Case 17.—Goldflam [7]. Male, aged 56; good family history, no serious illnesses. For twenty-one years has had attacks lasting a few seconds to minutes, dozens of times a day; he knows what is going on round him during the attack and often leans against something until it is over. He always feels sleepy and tired, but undertakes long business tours. About the same time as the sleeping attacks began, on raising his arm to strike his child he felt limp all over. Since then all sorts of emotional disturbances have caused similar attacks, mainly affecting the legs so that he sinks helpless to the ground. This condition remained much the same during the twenty-one years he was under observation.

Cases with Sleep Attacks only.

Case 18.—Leslie, W., aged 16, was admitted to the National Hospital, Queen Square, under the care of Dr. Hinds Howell, in 1925, complaining of sudden attacks in which he fell asleep. He had chicken-pox and measles in childhood, otherwise his health had been perfect; his father and mother, four sisters and two brothers, are alive and well; one sister used to walk in her

sleep. He did well at school and worked efficiently as a messenger in a city office.

The first attack of sleep came on after a hard day at the office, when he sat down in an armchair after supper to read; he tried hard to keep awake but was unable to do so; next day he fell asleep in his chair at the office while waiting for orders; since then he has had several attacks every day under the most diverse conditions, e.g., while eating his dinner or while talking to friends. He does not sleep while he is moving about actively, but now, whenever he is at rest, especially if he sits down, the desire to sleep comes on; at first he has a feeling of intense drowsiness, then his head falls forward, the arms hang limply at his side, the lids droop, and he is unable to remain awake, try as he will. In many of the attacks, although people around him think he is sound asleep, he knows what is going on and can repeat conversations that took place during the attack; he wakens easily if anyone touches him or calls to him sharply, but he cannot rouse himself; if undisturbed, he sleeps for several minutes; if he happens to be in a comfortable position, he sleeps for fifteen or thirty minutes. Between the attacks he feels quite well. He sleeps soundly throughout the night and finds it hard to wake up in the morning.

Whilst in hospital several attacks were observed; in one he fell asleep while talking to the matron; he knew what she was saying and tried to answer her but could not do so; then his head dropped, his eyes closed and he slept standing up for a few seconds; on another occasion he was overcome while helping a patient to dress; he sat down and slept for two or three minutes.

In this case there were no attacks on emotion. Physical examination revealed no abnormality. His memory is good and he is intelligent and alert. Blood and cerebro-spinal fluid normal; pituitary fossa normal on X-ray examination. The attacks became less frequent while resting in hospital, but after his discharge they became more frequent.

Case 19.—Goldflam [7]. Male, aged 33; good family history, no serious illnesses; at the age of 19 he began to fall asleep several times a day (duration of attack not given), especially if he sat down at rest for more than fifteen minutes, but also when standing, walking and teaching in class; in an attack he appears to be in normal sleep; he sees everything as through a fog, and hears everything as through a wall. He is easily wakened, when he feels fresh at once. In this case there is no mention of attacks on emotion, but I have accepted it as one of true narcolepsy because of the long duration without the appearance of any other disease in which attacks of sleep occur as a symptom.

Case 20.—Goldflam [7]. Male, aged 48; good family history, no other illnesses, always a heavy sleeper. For nine years he has had innumerable attacks of falling asleep in all circumstances; he knows what is going on and supports himself, e.g., against a wall, until the attack is over; he is doing strenuous work as a merchant. The first attack occurred immediately after a

blow on the head with an umbrella (? emotional factor). Here again there is no mention of attacks on emotion, but the long duration of the attacks appears to justify the inclusion of this case under the heading of true narcolepsy.

General Description of the Disease.

Etiology.

(*a*) *Sex.*—Of the cases I have included here seventeen are males and only three, my own cases, are females. Hitherto the only published female cases were two described by Nevermann [17] and by Kollewijn [12] of "narcolepsy in pregnancy"; but these were not cases of true narcolepsy, for sleep attacks alone occurred and they ceased after delivery. Among eleven cases (unpublished) seen by Redlich [26] two were females. It has been said that true narcolepsy is confined to the male sex, but my cases prove that females may also be affected.

(*b*) *Age at onset, duration and effect of treatment.*—The age at onset in the published cases included here varied from 13½ to 39 years, and averaged 23½ years; in my own cases the ages were 11, 12, 15, 20 and 35 years; Redlich states that it varied in his unpublished cases from before puberty to beyond the age of forty. In several reports it is stated that the patient had always been sleepy, and it may be that the onset is sometimes earlier than my figures indicate; nevertheless, the statement that the disease is one that begins at puberty is certainly incorrect.

The duration of the disease at the time the patients came under observation varied from six months to fifteen and twenty-one years.

During the time the disease had been present its severity was fairly uniform; my impression is that it persists with slight variations in intensity throughout life.

Many forms of treatment have been tried without success: bromides and other anti-epileptic remedies produce no favourable effect. Some have tried to diminish sleep during the day by making the night sleep more profound, others have given caffein and other drugs reputed to prevent sleep. Thyroid and various polyglandular preparations have also been used. In many instances the attacks became less frequent while the patients were resting in hospital, but they recurred with the original frequency soon after discharge.

(*c*) *Family and personal history.*—As a rule there is nothing in the family history of these patients to indicate that they belong to a neuropathic or degenerate stock; an aunt of Loewenthal's patient was a

paranoiac: the father of Henneberg's patient had tabes dorsalis; the father of Redlich's patient was an alcoholic; but in almost every case where careful inquiries were made it is stated definitely that there was no evidence that heredity is an important ætiological factor. Nor does anything in the personal history recur with sufficient frequency to justify its recognition as an exciting or contributory cause; a blow on the head is mentioned in Singer's and Goldflam's cases, but in the first it is probable that the fall was the result of the disease, and in the latter the blow was given by an umbrella.

Excessive nose-bleeding in childhood is noted in cases recorded by Mendel and Jolly.

I have made careful inquiries into the family and personal histories of my own patients; in each instance the stock was sound and the patient's previous health was remarkably good.

General Condition.

Mentally the patients were normal in almost every instance: Noack's patient was "slightly feeble-minded," otherwise there was no defect of intelligence or peculiarity of temperament. In several cases a full psychological or psycho-analytical investigation was made with negative results. The patients had worked with success as mechanics, schoolmasters, merchants, commercial travellers and in other occupations demanding considerable intelligence. In every case it is stated definitely that indications of epilepsy or hysteria were completely absent. Redlich was the first to draw attention to signs of ductless glands disorder in some of the cases. In two of his cases, in the cases of Kahler and of Jolly and in one of my own, the pituitary fossa was remarkably small. In Dercum's and Henneberg's cases the patient presented slight acromegalic signs; in the former the sella was large. In three of Redlich's cases and in those of Dercum and Stiefler, sexual development was delayed and the genitals were small. Redlich reports that in nine cases where a complete blood-count was made the lymphocytes were increased in six and the thyroid gland was enlarged in several cases; the findings in four cases examined by Abderhalden's method suggested ductless gland disorder in three. In my patient (F. W.) with a smal sella the periods are irregular and scanty; Olive P. is fat, her periods began early, but they are very irregular and she has long periods of amenorrhœa.

The cerebro-spinal fluid was normal in every case where this examination was made. Night sleep was normal in amount and

quality or excessive and very deep. Many of the patients felt tired and sleepy throughout the day.

The Attacks.

In most cases of true narcolepsy two kinds of attack occur; the patient is overcome by sleep or, usually as a result of some emotional disturbance, the muscles become flaccid and powerless.

For the sake of brevity I shall refer to these symptoms as sleep attacks and cataplexy.

Sleep attacks nearly always appear first and may precede the other kind by a year or more, but in cases described by Goldflam, Henneberg and Somer, cataplectic attacks occurred for several months before sleep attacks began. In one of my cases (F. W.) and in those of Gelineau and Somer, cataplectic attacks sometimes ended in sleep

Sleep Attacks.

(*a*) *Frequency and duration.*—The attacks vary greatly in frequency and duration in different patients but in each individual they are fairly constant; details so far as they are available are given in the following table:—

Author	Daily frequency	Duration
Löwenfeld ...	Every ten minutes	A few seconds
Redlich ...	Two or three	Five to ten minutes
Noack ...	Six	Five to forty minutes
Goldflam ...	Several	No note
„ ...	Innumerable	A few seconds
„ ...	„	Seconds to minutes
Stiefler ...	Three or four	A few minutes
Stöcker ...	Four or five	Ten to thirty minutes
Mendel ...	Two	Fifteen
Jolly ...	"Whenever he sits down to rest"	(No note)
Henneberg ...	Five or six	Fifteen minutes
Singer ...	Two or three	A few seconds to fifteen minutes
Adie 1 ...	Several while active: whenever she sits down at rest	A few minutes
„ 2 ...	Ten	A few minutes
„ 3 ...	One or two	Five or ten minutes
„ 4 ...	Whenever he sits down at rest	Two or three minutes
„ 5 ...	Several every day while working; whenever he sits down	A minute or two; up to half an hour if in a comfortable position

In the notes on the published cases it is frequently stated that the patient sometimes sleeps for an hour or more when the circumstances are favourable. Noack's patient once slept for thirty-six hours, Redlich's for twelve.

(*b*) *Circumstances in which sleep attacks occur.*—The attacks often occur in circumstances conducive to sleep, e.g., after a meal, during the mid-day rest, in warm weather or in a close room, but in every patient some have occurred under conditions by no means favourable for sleep, e.g., in the midst of an interesting conversation, during a game of cards, while walking in a busy street, while ploughing, riding or cycling, on the march, during bombardments, on listening-post duty where the penalty for sleeping is death, in fact in all conceivable circumstances. Captain X. once went to sleep while driving his car and woke to find the front wheels mounting a bank at the roadside; Singer's patient fell asleep while dancing; in Singer's case and in one of Fischer's (quoted by Redlich), attacks occurred during coitus.

Many patients have a definite aura; in some the attacks are said to come on without warning. My own patients all had warning of the attack and complained bitterly of the unpleasant sensations of intense fatigue that preceded it; two of them spoke of indescribable discomfort in the frontal region, "as if the head was going to burst," "as if the brain wants to expand." Some can resist the inclination to sleep for times that vary from a few minutes to half an hour, but try as they will they sleep sooner or later, and the longer it is deferred the more sound and the more prolonged is the sleep that almost inevitably follows. "I can ward it off for a time," one boy said, "but I am just packing it up for later on."

(*c*) *Condition during the attack.*—In almost all the published cases the author has seen his patient during an attack; as a rule the statement is made that it resembled exactly normal sleep. In some reports more detail is given, from which it is clear that the depth of unconsciousness varies considerably. Briefly the condition in observed attacks was as follows:—

Löwenfeld	...	Normal sleep, easily awakened.
Stöcker	...	True sleep, easily wakened by a call.
Stiefler	...	Normal sleep, easily wakened, Meyer's reflex present. (This reflex is absent after an epileptic attack.)
Redlich	...	Normal sleep, easily wakened; slight headache if wakened.
Jolly	...	Perfectly natural sleep, easily wakened.
Noack	...	Normal sleep, angry if wakened.

Singer	...	Normal sleep, sees and hears nothing while asleep, easily wakened.
Mendel	...	Normal sleep, hears everything, easily wakened, e.g., by raising lids to examine pupils.
Somer	...	Natural sleep; if he hears conversation he makes irrelevant remarks, which he recognizes as such, and is awakened by his feeling of annoyance.
Goldflam	...	Appearance of normal sleep, but he sees everything as through a fog and hears everything as through a wall, easily wakened.
,,	...	Normal sleep, but cannot be wakened, conjunctival reflex present, pupils small, reacting to light, eyeballs rolled upwards.
,,	...	Normal sleep, usually knows what is going on round him, but once in prison burning his soles failed to waken him.
Henneberg	...	Normal sleep, easily wakened as a rule but sometimes needs a good shake.
Gelineau	...	Normal sleep; the only way to waken him is to shake him violently.
Adie 1	...	Normal sleep, unconscious of surroundings, easily wakened, knows she has slept, wide awake at once.
,, 2	...	Normal sleep, unconscious of surroundings, easily wakened, feels as if she has been asleep in a stuffy room.
,, 3	...	Normal sleep, easily wakened.
,, 4	...	Normal light sleep, unconscious of surroundings, easily wakened, fresh at once.
,, 5	...	Normal sleep, is sometimes able to repeat what he has heard during the attack, but in some he is unconscious of his surroundings, wakes easily, wide awake at once.

The patient, as a rule, feels fresh on waking, and is wide awake at once; he knows he has slept and often remembers the content of his dreams.

Cataplectic Attacks.

These attacks may be brought on by almost any emotion; hearty laughter is the most potent cause, then anger or annoyance. Gelineau's patient had his first attacks on laughing heartily only, but later all sorts of emotions, pleasurable or not, brought them on; if when playing cards he found he held a good hand and was likely to win, or if in business he saw the prospect of a good deal, he felt a sudden weakness, his head fell, the limbs gave way and he sometimes fell asleep. If he

had an attack in the street he walked like a drunken man; when bystanders reproached him he was unable to reply; the more they mocked him the weaker he felt until he fell, evading traffic by a final effort; when a crowd collected, "as it does so quickly in Paris," and he heard sympathetic remarks he felt weaker still, and recovery was hindered; at the theatre, which he visited with great pleasure, the thought of enjoying himself caused him to have an attack as soon as he sat down. "His son wakens him if he goes to sleep; as soon as the play begins he follows it with interest and does not have an attack unless he laughs heartily or a sad incident affects him too much. If he becomes enraged he does not sleep while the passion lasts, but an outburst is always followed by sleep; if he sees two boys fighting and takes the part of one, his limbs become flaccid and he is unable to stand." This case is remarkable for the fact that most of the attacks of both kinds were brought on by emotion.

In one of Somer's cases both kinds of attack occurred separately, but sleep sometimes followed an attack on emotion; for example, the patient had an attack followed by sleep while he was recounting the painful circumstances in which his first cataplectic attack occurred.

My patient, F. W., had sleeping attacks alone during the first year; then cataplectic attacks began which for a time always ended in sleep; now she has frequent attacks of both kinds, but she rarely sleeps after emotion.

Condition in the Attack.

Descriptions of the condition during the cataplectic attacks are meagre, and in most cases are based on hearsay; they are rarely observed by a physician because the patient refuses to laugh heartily in his presence.

The statements made on the subject by the various writers are as follows:—

Löwenfeld	...	If he laughs heartily the muscles go slack and things fall from his hands; he holds on to prevent himself from falling; he grimaces, his jaw falls and he is unable to close his mouth.
Noack	...	When he is pleased he grimaces and protrudes his tongue; when he laughs heartily he moves his head, which falls to one side as if it were loose, the arms hang limply and the legs give way at the knees so that he fears he will fall; things always drop from his hands when he laughs; anger causes the same symptoms.

Somer	...	When he laughs his head falls forward, his knees give way, and he sinks slowly to the ground unable to move for about half a minute; if called upon to speak he mutters incoherently; he remembers the attack and everything that takes place during it.
,,	...	The attacks are caused by hearty laughter and other excitement. He had an attack while dressing—the head sank on the chest, the lids closed, the face was pale, the knees gave way, and he sank slowly to the ground, where he remained in a sitting position unable to move for about half a minute; when ordered to speak he stammered, but could not open his mouth properly; later he recovered his speech, then stood up and finished dressing. He always remembers everything that occurs during the attack; sometimes he is able to repeat words to order during the attack.
Singer	...	If he laughs he grimaces and his knees give way, but he does not fall; he does not lose consciousness.
Henneberg	...	If he laughs heartily the head falls forward, the jaw drops, the knees give way, and he has difficulty in standing; there is no dimming of consciousness.
Jolly	...	On laughing loudly the head falls forward, the jaw drops, and he has no power in his knees; he is unable to move.
Mendel	...	He can laugh heartily with impunity, but if he is angry the head falls forward and the knees give way.
Redlich	...	When he laughs the knees give way, he feels as if he will fall and things drop from his hands; he does not lose consciousness.
Stiefler	...	When angry or annoyed he gets a sudden feeling of helplessness; his knees give way, and he is unable to say a word.
Stöcker	...	Nothing happens when he laughs, but if he is suddenly called upon to perform a particular task his strength goes; sometimes if he clenches his teeth and tries hard he can resist the attack and continue working, but with diminished strength; the attack lasts less than a minute. When he larks with other boys he loses his strength, and the weakest can do what he will with him.
Adie 1	...	She opens her mouth, her head falls forward, the arms fall to her side, and the knees give way; she cannot move or speak but is fully conscious.
,, 2	...	"The lips and eyelids trembled, the head fell to one side, and she lay back on the pillow." (This attack ended in sleep.) In attacks that do not end in sleep she is fully conscious of her surroundings, but cannot move or speak.

Adie 3 ... "All the strength goes from me and I collapse; they think I am asleep because my eyes are closed, but I hear everything; I cannot move or speak."

„ 4 ... "I go floppy all over and have to sit down."

Several names have been used for these attacks on emotion, e.g., "chute ou astasie" (Gelineau), "kataleptische Starre" (Löwenfeld), "kataplektische Hemmung" (Henneberg), "plötzlicher Tonusverlust," "affektiver Tonusverlust" (Redlich) and "Tonusblockade" (Stern). I have considered many possible names for the use of English writers; a translation of the name proposed by Löwenfeld is unsuitable, as catalepsy and cataleptic are already in use with a different meaning; following Redlich I might speak of atonic attacks or tone-loss attacks on emotion, but I reject these because they tend to perpetuate the prevailing notion that all the symptoms in the attacks on emotion are explained by sudden loss of muscle-tone. Loss of tone would account for many of the symptoms but it does not explain some of them, e.g., grimacing, protrusion of the tongue and stammering, nor should it cause a patient to sink to the ground fully conscious but *unable to move a muscle or say a single word.* In all that follows I shall use the terms cataplexy and cataplectic for these attacks; they are non-committal in that they do not pretend to denote the mechanism of the attacks; they are not in general use for any other kind of sudden attack and they do suggest what is wanted, the idea of being overcome by emotion.

The movements that may occur in these cataplectic attacks are of considerable practical importance; they account, I think, for the frequency with which epilepsy is diagnosed in true narcolepsy. I have mentioned grimacing, protrusion of the tongue and stammering. Repeated movements of another kind may also give rise to error; the head may not fall forward or to one side at once and remain in one position, but may be moved to the erect position by repeated efforts only to fall again; or the outstretched arm may sink not in one movement but in a series of jerks. One of my patients (D. R.) described these events clearly; his efforts to overcome the defect in his muscles were mistaken for chorea at one hospital and for epilepsy at another. "I cannot go to the pictures now," this boy said, "because if I see anything funny I get an attack; my head flops about and people stare at me instead of looking at the pictures." I have found no previous reference to repeated movements of this kind; their importance for diagnosis is obvious.

In contrast with sleep attacks, which are usually irresistible, some

patients learn to prevent cataplectic attacks by refusing to laugh heartily; my patient, O. P., explained this to me clearly, and Noack reports that although his orderlies saw many attacks he saw none as the patient refused to laugh in his presence. As no patient has been examined by a competent neurologist while in the cataplectic state we do not know exactly to what extent the patient is paralysed or how the distribution of muscle-tone is altered. It is certainly interesting and perhaps of some significance that the symptoms mentioned by the patients refer to muscles that counteract gravity, the jaw drops, the head falls loosely and so on; defects in these groups would be most obvious and it may be that the loss of tone is general; if it is elective it would provide an interesting clinical corresponding opposite of decerebrate rigidity. As we shall see later the structures whose functions are disordered in narcolepsy are close to the red nucleus; a positive lesion in this nucleus would cause an elective tone loss of the kind that is probably present in this disease, but it is useless to speculate in the absence of exact data.

The Nature of the Attacks.

In this account of the attacks in true narcolepsy I have found it convenient to consider the two "kinds" of attack separately. In this I have followed other writers on the disease, but I cannot follow them when they infer that the two kinds of attacks are as distinct in nature as they appear to be on superficial examination; for close scrutiny makes it clear that every gradation occurs between mild cataplexy with no dimming of consciousness whatsoever to profound and prolonged sleep. For purposes of description and for didactic exposition one would be justified in giving the bald facts; two "kinds" of sudden attack occur, sleep attacks without cause and cataplexy on emotion. In these few words the features that distinguish true narcolepsy are named and anyone possessing this knowledge would be able to recognize a "typical" case. But for our present purpose a more searching inquiry is necessary. It may be that there are cases in which both kinds of attack always occur independently in a pure form, on the one hand sleep without any cataplectic symptoms, on the other attacks of pure cataplexy with complete retention of consciousness throughout; but I feel sure that these cases, if they exist, are rare. The "aura" of a sleep attack, the feeling of weakness and intense fatigue that so often precede the onset of sleep, is an expression of cataplexy, and when this "aura" constitutes the whole attack it is difficult to place it in either

category. My patient, Olive P., often has attacks of this kind; without any cause she is overcome by a feeling of weakness and excessive tiredness, so that it is difficult to move the limbs; this may or may not pass on to sleep. Stöcker says of his patient, "If he clenches his teeth and tries hard he can resist the attack and continue working, but with diminished strength; if he gives way his strength diminishes still further, he is unable to move the limbs and he may fall asleep."

Again, the depth of unconsciousness varies greatly in the sleep attacks: sees and hears everything while asleep, hears and remembers everything, sees everything as through a fog and hears everything as through a wall, usually knows what is going on around him; these are some of the statements that occur in descriptions of patients who were said to be in attacks exactly resembling normal sleep. These remarks apply to some of the attacks only; in others in the same patient sleep was moderately deep, so that firm shaking was necessary to waken him, or even profound. In the mildest attacks where the patient hears and remembers everything I suspect that it is the combination of immobility with closure of the lids that gives rise to the common statement that "his appearance was that of a person in quiet normal sleep." My patient, Mrs. C., told me that "they always think I am asleep; my eyes close at the beginning of the attack; I try to open them but cannot; I hear them saying that I am asleep; I try to speak but cannot move my lips or say a single word." My patient, L. W., at the beginning of a sleep attack unconnected with emotion, heard what they said and tried to answer but could not; then his head dropped, his eyes closed and he slept for a few seconds.

Some of the attacks, then, that have been called sleep attacks are perhaps better described as severe cataplectic attacks—transitions between cataplexy and sleep. On the other hand, while some patients undoubtedly have pure cataplexy without dimming of consciousness, many of the attacks that have been placed under this heading are also transitional; in several cases, including one of my own (F. W.), attacks on emotion ended in sleep. In some cases cataplectic attacks occurred alone for many months, then sleep attacks began with or without an emotional cause; in Gelineau's patient both kinds of attack nearly always came on with pleasurable emotion, not at other times; one of Goldflam's patients had both kinds of attack, cataplexy being sometimes connected with emotion and sometimes not.

These facts lead to the following conclusions: In typical cases two kinds of attack occur—sleep without cause and cataplexy on emotion;

but many attacks are transitional and do not fall readily into either category. Although sleep usually comes on without cause it may follow symptoms brought on by emotion; although cataplexy usually follows an emotional disturbance it may come on without cause. Hence the underlying mechanism is the same in all the attacks; essentially they are expressions of the same process differing only in degree. What this process is I shall consider later.

In three cases that I accept as examples of true narcolepsy sleep attacks alone are described. Attacks on emotion often follow sleep attacks after a considerable interval, as in my case (F. W.), and it may be that in my case (L. W.) where the duration of the disease is short they may appear later. In Goldflam's cases the long duration of typical sleep attacks without the appearance of any other disease to which they may be attributed causes me to accept them and admit that sleep attacks alone may occur in genuine cases.

So far I have written of "sleep attacks," taking it for granted that the condition of the patient in many of them was that of a person in normal sleep. I have done this because I am convinced that it is true, but it is right to mention that this opinion, though held by most writers on the subject, has not gained universal acceptance. Wendoveric [36] in a recent paper states that the sleep attacks in narcolepsy are distinguished from true sleep by the occurrence of "grelle Traüme," but this is certainly by no means constant or even frequent in narcolepsy and vivid dreams are common enough in normal sleep. The fact that patients with narcolepsy sometimes sleep while walking, riding and so on is of little importance. War experience teaches that a tired man can walk or ride in a semi-sleeping state which would soon pass on to normal sleep if the conditions were favourable; patients who complain of sleeplessness describe states transitional to sound normal sleep in which passing events are more or less appreciated and capable of recall. Goldflam has given particular attention to this point, and after careful observation of one of his patients he was able to state that the condition during the attacks was in every ascertainable way exactly that of normal sleep.

Patients with true narcolepsy, then, have sudden attacks in which they fall asleep; here we are dealing not with any qualitative change in the reaction of a human being to its surroundings, but merely with an exaggeration of events that occur in the state we call normal. A man who falls asleep on a warm afternoon after a good lunch, or one who sleeps during a dull discourse, is not held to be suffering from disease.

Individuals vary greatly in this respect. One of the most active of my colleagues drops off to sleep, just as a dog does, when he is sitting alone with nothing better to do. But patients with narcolepsy sleep not only under circumstances that invite sleep but also under the most unfavourable conditions; once the inclination is felt sleep is inevitable although it may endanger life. More than one case of narcolepsy was detected during the war when a man under arrest and liable to be shot for sleeping at his post was submitted for medical examination prior to his court martial. Most important of all, in narcolepsy sleep may follow hearty laughter and other emotional disturbances.

In these respects our patients so far overstep the arbitrary limits of the normal that we are justified in saying that they suffer from disease.

I have said that there is very little difference of opinion regarding the unity of the sleep attacks and normal sleep. Concerning the attacks on emotion opinions are still sharply divided. The expressions "helpless with laughter," "laugh—I nearly died!" "speechless with rage," and many others, remind us of the normal effects of emotion. That one of the patients I have described lost all his strength when larking with his mates, so that the weakest could overpower him, would not surprise a normal person who is ticklish. That another felt weak when called upon to perform a certain task would be understood by anyone who has suffered from ordinary stage fright or gone "over the top." Many must have experienced the effect of a sudden call for quick judgment when faced by imminent danger when motoring, and the curious feeling that pervades the body for the instant that elapses between thought and appropriate action. I once sat beside a driver who was so overcome by the sight of approaching danger, which he had ample time to avoid, that he sat helpless while I braced myself for the serious collision that followed. I suspect that many motoring accidents result from similar cataplectic attacks. The rabbit or bird "fascinated" by the snake is perhaps in the same condition, likewise the animals that sham death in the face of danger.

Curschmann and Prange [1] enumerate many of the well-known effects of emotion on the musculature of man and lower animals, and protest vigorously against the acceptance of cataplexy as characteristic of narcolepsy. "We must emphasize very strongly," they say, "that we see in affective hypotonia nothing characteristic of narcolepsy, but merely a widespread form of motor reaction to emotion that occurs in normal people."

The effects of emotion on normal persons are familiar to all, but

though uncontrolled laughter reduces many to a state of helplessness, this only occurs when they have more or less voluntarily "let themselves go," and we do not see people otherwise healthy in mind and body sink helpless to the ground unable to move for half a minute or more, *every time* they laugh with ordinary heartiness, nor do they ever fall asleep at these times as patients with narcolepsy sometimes do; normal people do not fall asleep when they see the prospect of good business or hold a good hand at cards, or study a stroke at billiards, or feel sad or gay at the theatre—it is not necessary to multiply examples. I am convinced that the effects of emotion on patients with narcolepsy, though undoubtedly akin to those in normal persons, so far differ from them in degree that they must be looked upon as pathological.

To my mind cataplexy in narcolepsy is as characteristic of the disease as the sleep attacks themselves. Given a case with sleep attacks alone the diagnosis is difficult, for sleep attacks indistinguishable from those of true narcolepsy occur as a symptom in many dissimilar diseases; but if definite cataplectic attacks are present as well the diagnosis is made certain, for the combination is seen in no other condition whatsoever. I shall deal with localization and the mechanism of the attacks in a later chapter.

Diagnosis.

Epilepsy.

To one unacquainted with the manifestations of true narcolepsy a description of the symptoms by a patient or his friends would certainly suggest epilepsy. "He grimaces, the head falls forward, the limbs become slack and he sinks to the ground," might well be an account of a mild epileptic seizure; moreover, epileptics often sleep after an attack, and as it is perhaps true that irresistible sleep is occasionally an epileptic equivalent, the statement that the patient fell asleep at odd times would not divert the uninitiated physician from his false diagnosis. But to one familiar with both diseases confusion is hardly possible. Even if we admit that sudden attacks of apparently normal sleep occur in epilepsy, it cannot rightfully be maintained that these attacks may be the only manifestation of epilepsy throughout long years—unless we alter our definition of epilepsy.

It has happened in several cases that cataplectic attacks occurred alone for a few months before the sleep attacks began; in these cases the diagnosis of epilepsy could only be made if the history were taken carelessly, for a most important feature of idiopathic epilepsy is that

the attacks come on without apparent cause, whereas in narcolepsy the cataplectic attacks are "reactive," i.e., there is a definite exciting cause, namely, emotion.

In epilepsy, as a rule, the disease soon assumes a severe form in young patients with frequent minor seizures who do not respond favourably to appropriate remedies; in narcolepsy the attacks are often very frequent, anti-epileptic remedies have no effect upon them and the attacks go on with unaltered severity for years. In epilepsy mental deterioration and psychical defects are characteristic sequels that appear soonest in its victims who have frequent abortive seizures; narcolepsy, in spite of its long duration and the frequency of its attacks, does not impede mental development or give rise to psychical defects. In epilepsy the first major attack is rarely delayed more than a few years; patients with narcolepsy have been observed for periods of fourteen, fifteen, and twenty-one years; in no case was there a convulsive attack of any kind; in no case was there a family history of epilepsy. These—I need not mention others—are differences which cannot be ignored. I have perhaps laboured this point somewhat, but there is some justification because it is still stated in textbooks that "some of the cases (of narcolepsy) are hysterical, some epileptic." My own mind is quite clear on the matter; narcolepsy and idiopathic epilepsy are not the same because in narcolepsy some of the attacks are reactive. In genuine epilepsy the attacks are never reactive; this feature alone is sufficient to show that the two conditions are fundamentally distinct.

Pyknolepsy.

I have defined pyknolepsy elsewhere as "a disease with an explosive onset between the ages of 4 and 12 years, of short, very slight monotonous epileptiform seizures of uniform severity which persist for weeks, months or years, uninfluenced by anti-epileptic remedies, without impeding normal, mental and physical development and ultimately cease spontaneously, never to recur." In this disease, which is peculiar to children, the attacks consist of an inhibition of the higher psychical processes lasting from five to ten seconds; the power of speech and of voluntary movement is in abeyance but automatic movements are retained; the child stands with the limbs relaxed, staring vacantly; the lids may flicker, the eyeballs may roll upwards, but there are no convulsive movements and consciousness is never entirely lost. I have seen many of these attacks. They are indistinguishable from *petit mal*, they do not resemble normal sleep and there is never any "chute

ou astasie," no dropping of objects, no sinking to the ground as in narcolepsy.

It is unfortunate that Friedmann [5] who first described this disease used the expression "short narcoleptic attacks," for this has caused great confusion among German writers, many of whom still agree with Friedmann that the short attacks in pyknolepsy are of the same nature as the sleep attacks in narcolepsy and describe the two diseases under one heading.

Pyknolepsy begins between the ages of 4 and 12 years and usually terminates spontaneously in a few months or years, narcolepsy rarely begins before puberty and may persist throughout life. The attacks of pyknolepsy in no wise resemble sleep; they last a few seconds only; one kind of attack alone occurs and it comes on without cause, never as a result of emotional disturbance. Except that attacks occur in both diseases, there is, so far as I can see, but little similarity between them. Certainly the differences justify a distinctive name for each.

Hysteria.

For those to whom "hysteria" and "functional nervous disorder" are more or less synonymous terms, the symptoms in narcolepsy may be hysterical, but if "hysteria is a pathological state manifested by disorders which it is possible to reproduce exactly by suggestion in certain subjects and can be made to disappear by the influence of persuasion alone" (Babinski), then there is certainly no connection between them, for suggestion plays no part in narcolepsy and counter-suggestion has been tried without avail. There is never anything hysterical in the ordinary sense in the psychological make-up of patients with narcolepsy, they never suffer from the recognized manifestations of hysteria, and I am quite unable to agree with those who consider that some of the cases are hysterical, some epileptic.

Lachschlag.

In this condition, first described by Oppenheim [19], patients fall unconscious on laughing heartily. I have seen one patient only with this symptom. In my patient, as in Oppenheim's, no other kind of attack occurred; in particular, no sleep attacks. I have not made a special study of these cases, but, so far as I know, the patient is always deeply unconscious, and sleep attacks apart from emotion never occur. For these reasons I think that Lachschlag should be looked upon as distinct from narcolepsy.

Other Conditions in which Excessive or Untimely Sleep occurs.

Narcolepsy has been described in a number of unrelated conditions. Fat people, as in the classical case of the Fat Boy in "Pickwick," are inclined to drop off at odd times; obese patients with pituitary disease are often somnolent; one of my patients frequently fell asleep for a few seconds while she was under examination. Dercum [2] wrote a paper on "Profound Somnolence or Narcolepsy" in a patient with pituitary disease, and many others have referred to the frequency of somnolence in these cases. The tendency to sleep during the day after an attack of encephalitis lethargica has been described as "narcolepsy after encephalitis lethargica," and I have seen the name narcolepsy applied to the prolonged sleepy state that occurs in the early stages of this disease. Many patients with cerebral tumour are somnolent; some have what one of my patients called "dog-naps" during the day, and the tendency to sleep at odd times is often very noticeable. But in these conditions, and in others where excessive or untimely sleep occurs, the patient usually presents some evidence of the disease of which sleepiness is a symptom, whereas true narcolepsy occurs in persons who are otherwise healthy. In true narcolepsy characteristic attacks occur on emotion. This *never* happens when sleep attacks are merely a symptom of some other disease.

Nomenclature.

For various reasons a number of names have been suggested to replace the original name that Gelineau applied to his case.

Singer objects to narcolepsy because, like narcosis, it suggests artificial sleep; he proposes the name hypnolepsy in its stead.

Curschmann and Prange agree with Walther that the name narcolepsy should be abandoned because it suggests some connection with epilepsy. Their alternative is Einschlafsucht, but we have "sleeping sickness" and "sleepy sickness" already, and an English translation of their name would create further confusion. One objection to the name narcolepsy is that Friedmann called the attacks he described in children "short narcoleptic attacks." For English writers, at least, this difficulty should not arise, because the name pyknolepsy, which I recommended for Friedmann's disease, is gradually being adopted in this country.

It is unfortunate that narcolepsy is used now for a symptom common to many dissimilar conditions; this is, perhaps, a good reason why a

new name should be invented to designate a disease *sui generis;* nevertheless, I am strongly in favour of retaining the name narcolepsy for Gelineau's disease. Confusion would be avoided if we distinguished between the true narcolepsy of Gelineau and symptomatic narcolepsy.

Theoretical Considerations.

Narcolepsy and Pavlov's Researches on Sleep.

Piéron, in his book, "Du Sommeil," concludes his critical analysis of the more important theories of sleep with the following words: "En somme, parmi les théories il en est qui sont nettement contredites par les faits. . . . Il en est dont on peut dire qu'elles ne sont pas suffisamment explicatives . . . ou qu'elles restent purement hypothétiques comme la théorie de l'inhibition complétée ou non pas la conception d'un mécanisme protecteur. Est-il alors possible d'édifier une théorie toxique qui soit pleinement satisfaisante? . . ." Piéron elaborated a toxic theory, but to make it "pleinement satisfaisante," he was forced to think of "*some kind of inhibitory mechanism whose existence has never been demonstrated.*"

"La notion d'inhibition," he says, "n'est pas physiologiquement demontrée pour les centres encéphaliques supérieurs." This, as I shall proceed to show, is no longer true, for since Piéron wrote these words Ivan Pavlov [20] has demonstrated the existence of an inhibitory mechanism in the cerebral cortex, and has done much to explain the nature of cortical sleep.

Pavlov has truly said that "when the physiologist begins to study the highest parts of the central nervous system his methods change; he ceases to observe the reaction of the organism to external stimuli, and instead of describing phenomena in terms of physiology he introduces psychological ideas derived from his own consciousness." The resulting confusion is great; indeed, it is almost impossible for a working neurologist to think clearly about the functions of the highest centres because the counters of thought—the words he must employ—are often of psychological origin and for the most part meaningless. My study of Pavlov's work has shown me that it is possible to correlate changes in the organism, which appear at first sight to be most intricate and beyond the powers of analysis, with external stimuli; further, that the phenomena may be investigated by physiological methods and the results expressed in purely physiological terms. I am tempted to enlarge on the significance of Pavlov's remarkable work,

but I must confine myself to that part of it which has a direct bearing on my thesis.

For the development of my argument it is necessary to refer very briefly to "conditioned reflexes."

In studying the activities of the highest cerebral centres we can distinguish reflex activities with nervous connections present at birth and associated reflexes which appear during life. If indifferent stimuli of any kind frequently accompany a stimulus which evokes an inborn reflex, these stimuli by themselves soon begin to evoke the same inborn reflex by "association." These associations are true acquired reflexes which can be investigated by physiological methods. Pavlov calls the inborn reflexes "unconditioned" and the acquired reflexes "conditioned." From the moment of birth paths for conditioned reflexes are constantly being laid down; but the response to conditioned stimuli is not inevitable, for if it is untimely, or out of touch with reality, it may be inhibited. The following examples will explain my meaning.

If an indifferent stimulus, say a certain sound, regularly precedes a meal by a certain interval, this sound soon begins to evoke the normal response to the presence of food in the mouth—the secretion of saliva. If, after the conditioned reflex is firmly established, the stimulus is given, but food is withheld, the sound gradually loses its effect on repetition until no response is obtained, i.e., the reflex is inhibited. This inhibition disappears spontaneously after a time if the animal is left alone and the conditioned response will be obtained again, say next day. This phenomenon for which no satisfactory name exists in English may be called *temporary suppression or eclipse of the conditioned reflex*. (The German word which Pavlov uses is "Erlöschen," but this means obliteration, to be extinguished, to go out, to die out, to expire, suggesting permanent obliteration. A word is required which makes it clear that the reflex is not abolished, but merely temporarily suppressed.)

Again, in an instance where food regularly follows the sound in five seconds, and the conditioned response begins at the third second; if the procedure is altered and food follows after an interval of three minutes, at first the conditioned reflex disappears quickly; on repetition of the sound it reappears, but only during the third minute. In the earlier stage the stimulus loses its effect and the last part only is active. This is also an inhibition. I shall refer to it as *delay of the conditioned reflex*, or more briefly as *delay*.

If another stimulus, say mechanical stimulation of the skin, is combined with an effective conditioned stimulus (e.g., a sound), and

the animal receives no food after a combined stimulus, then in this combination the sound loses its effect, but still retains it when it is given alone. This is also an inhibition. I shall call it *conditioned inhibition*.

Finally, if mechanical stimulation of a point on the skin is made an efficient conditioned stimulus, then similar stimulation of surrounding parts will also evoke the reflex; the nearer the original point the more powerful the response. If now on repetition food is always given after stimulation of the original point, but never after stimulation of neighbouring parts, the latter gradually lose their power to excite. This I shall call *differential inhibition*.

These different forms of inhibition—eclipse, delay, conditioned and differential—are grouped together as internal inhibition. In passing I cannot resist the temptation to refer to the apparent complexity of these reactions, especially differential inhibition. They are the same as many complicated reactions, in performing animals for example, which seem to be expressions of high intelligence and considerable reasoning power. But they are matters of reflex and inhibition; they can be weighed and measured; they obey rigid physiological laws.

I must now consider the relation of internal inhibition to sleep, and give evidence for the belief that sleep and internal inhibition are subserved by the same mechanism.

From the beginning of his researches on conditioned reflexes, Pavlov was greatly hindered by somnolence and sleep which overcame his animals during the experiments. Animals chosen especially for their liveliness and wakefulness when free succumbed readily, and sleep often terminated the experiment before the observation was complete.

It would happen, for example, after a good conditioned reflex had been established, that the animal became somnolent or fell asleep during the time that the conditioned stimulus was active. Sleep was often so profound that firm prodding was required to dispel it from an active and greedy animal that had not been fed for twenty-four hours. In one instance a good conditioned reflex had been established; food followed the stimulus in ten seconds and the animal gave a very active secretory and motor response during the ten seconds between stimulus and food. But when food was withheld for sixty seconds a remarkable change occurred; the dog became sleepy during the waiting period, the conditioned response disappeared, and the dog that had never slept in the experimental stall before fell asleep every time the stimulus was repeated.

The same tendency to sleep was seen during another series of experiments in which conditioned reflexes were not used. When a new indifferent stimulus is given to an animal it responds by placing its receptors in the best attitude for receiving the impression; it looks towards a light, it cocks its ears in the direction of a sound, and so on. Pavlov calls this reaction the orientation reflex. If such a stimulus is repeated at frequent intervals the reflex diminishes steadily until it disappears, and if fresh dissimilar stimuli are not given the animal becomes somnolent or falls asleep. If this test is repeated several times with the same stimuli the animal can be made to sleep with absolute certainty. Special investigations by one of Pavlov's pupils have shown that this gradual failure to react to the repetition of a single stimulus follows the laws governing eclipse of a conditioned reflex, and it is almost certain that the mechanism is the same in both phenomena.

These and many similar experiences convinced Pavlov that the sleep that obtruded itself so persistently was something more than an annoying complication in his experiments, and in the end the problem of sleep itself engaged his particular attention.

After testing and considering various hypotheses during the course of ten years' work, he finally reached the conclusion that sleep and the internal inhibition that he had described in his work on conditioned reflexes were one and the same process. "With this conclusion," he says, "everything agrees that we have learnt during twenty years' work on conditioned reflexes," and special researches based on this conclusion have served to confirm it.

The main factor involved in this hypothesis is that every more or less prolonged stimulus to the cortex, whatever its nature and however strong it may be, if it is not accompanied by stimuli to other parts, or if it is not displaced by other stimuli, leads inevitably to somnolence and sleep. The conditioned reflex, even when it concerns the most potent of all stimuli—food—leads to sleep if it plays on an isolated spot on the cortex without being displaced by the mass stimuli that accompany the act of taking food. The same holds true even when the conditioned reflex that calls forth the feeding reaction is aroused by a very powerful electrical stimulus. That monotonous stimuli produce somnolence is of course well known, but before Pavlov illuminated this field it had not been made the subject of scientific research.

I have already given an example of sleep with delay of inhibition. Without going into detail I can say that sleep also occurs during

experiments on obliteration and on conditioned and differential inhibitions. Further, it is possible to observe the transition of inhibition into sleep and the reverse, the replacement of inhibition by sleep and summation of sleep and inhibition. As these phenomena supply convincing proof of the essential sameness of inhibition and sleep, I shall give a few illustrative examples.

Food is given to a dog thirty seconds after the conditioned stimulus; the secretion of saliva begins from five to ten seconds after the conditioned stimulus begins; the experiment is repeated for days, weeks and months, food always being given after the same interval. In the course of time the latent period of the conditioned reflex gradually increases to fifteen, twenty or twenty-five seconds, until it reaches to within a second or two of thirty seconds; finally, no effect is obtained, and at this point the animal becomes motionless or falls asleep; in this instance inhibition has passed into sleep. The reverse result is seen in a dog where a delayed inhibition is worked out with an interval of three minutes between the conditioned and unconditioned stimuli, the first part of the interval being active and the latter part inactive. In experimenting upon such an animal it may happen that at first it becomes sleepy as soon as the conditioned stimulus is given, only the last part of the interval being active. On repetition the active period gradually increases while the sleepy period diminishes *pari passu* until at last sleep gradually disappears. Here sleep has gradually given way to pure inhibition. The same change from inhibition to sleep has been observed during observations on the orientation reflex.

It has been observed during the investigation of delay, where the unconditioned stimulus follows in thirty seconds, that an animal, previously wakeful, falls asleep as soon as the conditioned stimulus is given, and remains asleep for twenty-five seconds, when it wakes and gives a strong reaction. It is obvious that in this case sleep has replaced inhibition and behaves in regard to onset and ending in exactly the same way as pure inhibition. In other cases it was equally clear that a summation of sleep and inhibition had occurred. All these facts enforce the conviction that internal inhibition and sleep are one and the same process.

At first sight this may seem strange, for internal inhibition occurs in the wakeful state; it is an expression of activity of the cortex, and shows the finest adaptation to stimuli from without, whereas sleep is essentially a condition of inactivity and rest for the cortex. But this difficulty is easily overcome if we look upon inhibition as *a partial and*

strictly localized sleep confined within narrow limits by an opposing process of stimulation, while sleep is inhibition which has spread throughout the cerebral hemisphere and to subcortical centres.

Guided by this explanation it is easy to understand the cases I have just described; sometimes inhibition spreads widely and the dog sleeps, sometimes it is diminished and sleep disappears. In the case, for example, where sleep was gradually replaced by pure inhibition, it is clear that the process of excitation gradually narrowed the areas under inhibition until sleep disappeared; in other words, a condition of equilibrium was attained which corresponded to reality.

From this we see that if we wish to limit inhibition and prevent it from passing into sleep, or if we wish to displace sleep by pure inhibition, we must produce new points of excitation in the cortex which will counteract inhibition and check its spread. In practice this succeeds admirably. In experimental work, where sleep begins to interfere with the tests, new conditioned reflexes are worked out with stronger stimuli, so that sleep is abolished and the original reflex which had become feeble is restored to full strength. In everyday life we constantly apply the same method to ourselves when we become sleepy. We abolish inhibition by building a new point of excitation in the cortex. We do not express it in these words, however; we are more likely to say, "I had to pinch myself to keep awake."

We know that repeated monotonous stimuli favour sleep; we know that a new stimulus will waken us when we are feeling sleepy. At every moment during the waking state the cortex is receiving innumerable stimuli of many kinds which may or may not evoke certain reactions. The vast majority of these reactions are purely reflex; they are associated reflexes acquired during life; we react to the stimuli according to the meaning we have learned to attach to them during life—they are conditioned reflexes. But we do not react at once to every stimulus we receive; by inhibition the reaction may be delayed or suppressed, but every time a reflex is delayed or suppressed an inhibitory mechanism is set in motion which is sleep in a limited area of the cortex; once started this process tends to spread, and if unchecked will extend throughout the cortex and produce sleep; in the waking state bounds are set to this spread of inhibition by the constant arrival of fresh dissimilar excitations.

This brief account of Pavlov's work gives an inadequate idea of the enormous number of facts that he has recorded which confirm his main thesis—sleep is internal inhibition. In this brilliant conception

we see a vivid and beautiful illustration of the principle of economy; for if sleep and inhibition are the same, then the mechanism that subserves the highest manifestations of life and renders possible the minute adjustments and endless adaptations of the organism to external changes is based upon a state of inactivity of the most precious elements of the body, the nerve-cells of the cerebral cortex.

I think the phenomena in narcolepsy, a disease in man, give strong support to Pavlov's conception of the mechanism of sleep based upon the results of his experiments on lower animals. I have attempted to show in earlier paragraphs that the two "kinds" of attack in narcolepsy are manifestations of the same process, and that every gradation is encountered from slight and local cataplexy to profound and prolonged sleep. A man raises his arm to strike his child but the arm falls limp and powerless to his side: another, as a result of some emotional disturbance, feels weak but is able to stand with support until the attack is over, or he sinks to the ground but is then able to move his limbs and speak; another falls motionless and speechless but fully conscious; another falls and passes into light sleep, during which he is more or less conscious of his surroundings and wakes in response to a call or a light touch; another wakens when shaken roughly; another does not wake up even when a hot iron is applied to his soles.

If the sudden loss of power in the arm in the first case and the sudden loss of tone and power in the intermediate cases are results of inhibition—I know of no other explanation—then the sleep of varying intensity in the other cases is also due to inhibiton; sleep and inhibition are one and the same process.

On the other hand, many of the curious features of narcolepsy become intelligible when viewed in the clear light of Pavlov's researches. Without their aid it is impossible to understand the dissimilarity in the factors that favour the onset of sleep attacks; it is not surprising that patients sleep sitting before the fire, after a heavy meal, in a warm room, during the rest hour, riding in a train and in similar circumstances; but why do they sleep at work in a factory, cycling, dancing, on the march, and in other circumstances by no means conducive to sleep in normal people? Apparently the attacks are favoured first by a lack of extraneous stimuli, and, secondly, by monotonous stimuli. Even a painful stimulus, such as a powerful electric shock, produced sleep with certainty in Pavlov's dogs if it was repeated, and no extraneous dissimilar stimuli reached the animal's cortex; the receptive point in the cortex became fatigued—it slept, and

inhibition spread unchecked by fresh stimuli to produce general sleep; *any* monotonous stimulus then favours sleep, and sleep in narcolepsy is favoured by monotonous movements. Several patients, including one of my own, fell asleep while cycling; one of my patients always went to sleep when he attempted to do a certain monotonous task in a factory—perhaps fatigue from the frequent repetition of the same movement explains sleep while walking, riding and dancing. In the extreme cases where it came on during coitus it seems more probable that sleep complicated an attack on emotion.

Again, it was difficult to understand at first why the patients were unable to resist sleep and yet could almost always be wakened with extreme ease; patients overwhelmed by sleep which they could not resist, try as they would, were wakened when the lids were raised to examine the pupils or by a slight touch or gentle call; sometimes they had succeeded in warding off sleep for several minutes, or even for half an hour; but during this time they had a feeling of extreme drowsiness and fatigue; "the brain felt as if it wanted to expand"; "it felt as if the head was going to burst"; yet, when wakened from their sleep, however short, they felt fresh and wide awake at once!

The explanation is simple: inhibition was dispelled at once and completely by a fresh excitation from without, exactly as it was in Pavlov's experiments. "Nothing I could do myself would keep me awake, but a touch or a call or a bump against something woke me up at once." One of my patients said: "I was marching along with the scouts one day when I began to feel sleepy; it was an awful feeling; I was just going off when a boy said: 'Have you got a knife, Dennis?'; this woke me up, and my head felt clear at once." These statements reminded me of an experiment of Pavlov's that was spoiled by sounds made by an attendant scraping snow from the doorstep; careful arrangements had been made to eliminate extraneous stimuli, and the animal was just passing into sleep under the influence of a monotonous stimulus when the unexpected sound woke it at once.

I repeat, then, that many of the hitherto unexplained features in narcolepsy become comprehensible when correlated with Pavlov's discoveries; the tendency to sleep when few stimuli reach the cortex or when the stimuli are monotonous; the transitions from cataplexy to sleep, the ease with which the patient is wakened by a fresh stimulus, the immediate and complete wakefulness of a patient so awakened—all these had their counterparts in Pavlov's dogs.

My submission is that all the attacks in narcolepsy are due to

inhibition, not only the "tone-loss attacks on emotion," but the sleep attacks as well.

Narcolepsy after Encephalitis Lethargica.

It is convenient to interpolate here a description of two cases in which the symptoms of true narcolepsy followed an attack of encephalitis lethargica, as these cases have influenced me in forming the conclusions I shall set down later concerning the localization of the disturbance in true narcolepsy.

Case 1.—Donald R., now aged 17, had an attack of encephalitis lethargica in 1923, with fever, sleeplessness, delirium and jerking of the limbs, followed by double vision, restlessness at night and excessive sleep during the day. He recovered in about three months sufficiently to get up and go about, but never became the same boy again; his features were expressionless, his movements were slow, he became very stout, he was bad tempered and argumentative and still apt to drop off to sleep during the day.

By the middle of 1924 he had improved in many ways; he was sleeping well at night, he had lost the mask-like face, and his vision was normal, but from that time he has suffered from attacks that trouble him excessively. In his own words "it is fatal" to sit down or to perform a monotonous task, for if he does so he goes off to sleep at once; he cannot sit down to read a book because he sleeps before he reads a page; he dare not sit down in a bus or tube for fear of passing his destination. At his work in a factory he has permission to leave his bench to walk about in the fresh air whenever he likes because a monotonus task makes him sleep and rapid movement may avert it; as a rule, however, the sleep comes on sooner or later; "if I delay it by moving about I am just packing it up for the future." At the beginning of an attack the feeling of drowsiness is overwhelming and "nothing I can do myself will keep it from getting worse, but a new voice or something outside will wake me up."

The other attacks are even more troublesome. If he laughs his knees give way and he falls to the ground. "At the scouts' camp the boys used to amuse themselves by making me laugh and then running away leaving me helpless on the ground." "I cannot go to the pictures now because if I am amused my head flops about and people look at me instead of the pictures; if I am excited or angry the same thing happens; my head falls down, it is all floppy and wobbly as if the neck were loose; I should drop a cup of tea from my hands; if I were standing up my knees would give way and let me down." There is no dimming of consciousness in these attacks and they never lead to sleep.

In other respects the boy is perfectly well physically; he presents none of the common residual ocular and motor signs of encephalitis lethargica; his mother, however, says that his memory is not very good and that he is not such a "nice" boy as he used to be. The attacks are gradually becoming less frequent, and he is beginning to lose weight, but he is still much fatter than he used to be.

To hear this boy describe the conditions under which his sleep attacks occur and the things that prevented them, was like reading a description of some of Pavlov's experiments on sleep. A monotonous task caused sleep; nothing arising from within could prevent sleep, exert himself as he would, but "a new, fresh voice" (he used these words himself) or anything coming from without woke him at once.

The account of the acute attack of encephalitis is so clear that there can be no doubt about the diagnosis; before this attack he was perfectly well. He now presents none of the usual sequels except a change of temperament—not the slightest degree of Parkinsonism, no subjective or objective ocular symptoms. Nevertheless I think we must regard his present condition as a sequel of encephalitis lethargica. The alternative is to look upon this as a case of idiopathic narcolepsy arising in a boy who happens to have had encephalitis lethargica. I could not accept this explanation when this case was unique in my experience; my doubts have been set at rest because Stiefler [33] has described a similar case.

Case 2.—Stiefler [33]. A man, aged 20, had epidemic encephalitis in February, 1923, with fever, headache, neuralgic pains, double vision and other characteristic symptoms. In May, 1923, he began to have from ten to twenty attacks daily in which he fell asleep in spite of all his efforts; he slept sitting, standing, walking, at work, at meals and in the middle of a conversation; in the attack his appearance was that of a person in normal quiet sleep; he was easily roused and after rubbing his eyes and perhaps yawning he was wide awake again. If he laughed heartily or felt angry he lost control of his limbs; he could not move them at will and the knees sometimes gave way so that he fell to the floor where he sat for several minutes unable to speak a word; throughout the attack his head felt clear and he was fully conscious of his surroundings; he gained over 2 stone in weight after his illness. In the autumn of 1923, apart from obesity and the attacks, he was perfectly well and careful examination revealed none of the late motor or other signs of encephalitis lethargica, except a slight defect in the contraction of the pupil on convergence. By the end of the year sleep attacks were less frequent and the attacks on emotion had ceased almost entirely.

Several features common to Stiefler's case and my own are worthy of note; in both there was a remarkable increase in weight, the attacks became less frequent with the passage of time and at the time the patients came under observation they were almost entirely free from the common late sequels of the primary disease.

I often wondered why the symptoms of true narcolepsy—a functional disorder—never follow an organic lesion. According to a

general principle that I have found of great value, I expect to find for every expression of disordered cerebral activity due to organic disease a corresponding syndrome from functional disturbance and vice versa. These cases provide evidence in support of the general principle; in them, I imagine, an organic lesion caused symptoms that are usually due to a functional disturbance in the same situation.

Narcolepsy and the Pituitary 'Tween-Brain System.

In this chapter I shall give the evidence that supports me in my belief that narcolepsy is primarily a disorder of an intimately connected endocrine-nervous mechanism, the pituitary 'tween-brain system I shall call it, that is formed by the pituitary body and certain vegetative centres in the base of the 'tween-brain.

Anatomical, experimental and clinical considerations all support the notion that such a system exists, and I think that the facts in narcolepsy may be added to those gained from a study of diabetes insipidus, dystrophia adiposo-genitalis, and many other metabolic disturbances that serve to prove that the same symptoms and syndromes may be caused by disease strictly confined to the glandular or nervous part of this system.

The pituitary body is richly supplied by nerves; the anterior lobe receives sympathetic fibres from the carotid plexus; a stout bundle of fibres leaves a group of cells in the floor of the 'tween-brain and passes down the infundibulum to the posterior lobe. Pines [23] calls the centre from which these fibres arise the nucleus hypophyseus and identifies it with the nucleus supraopticus of other writers; reversely pituitary secretion reaches the vegetative centres in the 'tween-brain, not only by the blood-stream but certainly in the cerebro-spinal fluid; thus the arrangements allow the gland to be stimulated from vegetative centres and the activity of these centres to be influenced by glandular secretion.

Karplus and Kreidl first showed experimentally that various disturbances in sympathetic innervation could be produced by stimulating different parts of the base of the 'tween-brain, and later investigators have obtained results which prove that centres exist in this part whose integrity is essential for normal temperature regulation, fat, water and sugar metabolism, and sex gland activity.

Destruction of the temperature-regulating centre which is situated near the tuber cinereum renders animals poikilothermic, and it is impossible to cause a rise of temperature in them by infection, or by any of the many methods by which fever may be produced experimentally

in normal animals. Further, it has been shown by many investigators that minute lesions confined to the 'tween-brain and certainly sparing the infundibulum and hypophysis may produce transient glycosuria or polyuria and be followed by obesity and atrophy of the genitals.

Clinical evidence, for example the behaviour of the temperature in encephalitis lethargica, confirms these results; the sudden rises of temperature that occur in all stages of this disease without corresponding increase in other symptoms, are explicable on the assumption that inflammation has spread to a particular centre in the 'tween-brain (Economo). I am convinced from my own observations that irregular pyrexia may be the only symptom for many months in patients who ultimately develop the Parkinsonian syndrome. In two cases where no history of an acute attack was obtained the diagnosis of tuberculosis had been made. Further, moderate or extreme obesity, slight or very severe diabetes insipidus and dystrophia adiposo-genitalis are well-known sequels of encephalitis lethargica, a purely nervous disease, and of many other conditions affecting the infundibular region, where, however, it is difficult to prove that the pituitary gland and its effluent channels are intact.

These facts—clinical and experimental—prove that many vegetative disturbances can arise in the 'tween-brain. They have caused some writers to refer to the symptoms we are considering as 'tween-brain symptoms and to deny their possible pituitary origin. At the last neurological congress in Paris, for example, Camus and Roussy maintained that diabetes insipidus is always of 'tween-brain origin. I do not think this attitude is correct. A case of mine has been published by Piney [24] where the diagnosis of secondary deposit of carcinoma in the posterior lobe of the pituitary body was made by me during life and confirmed by him after death, in a woman who had severe diabetes insipidus following removal of a breast for cancer. Schiff [27] states that Maronon collected thirty-two cases in which lesions strictly confined to the posterior lobe caused polyuria; Simmonds [28] has described several cases like my own. Those who deny that diabetes insipidus may result from pituitary disease ask why this is not more frequent, and why with an increasing lesion the polyuria may cease; the reason seems to be that polyuria occurs when the posterior lobe only is affected; if both lobes are damaged there is no polyuria, and if spread occurs to the anterior lobe it ceases (Hann) [8].

In the normal regulation of temperature the pituitary body certainly

plays a part, for it has been shown that extirpation of the gland or division of its stalk produces exactly the same result as does injury to the centre in the 'tween-brain; injections of pituitary extract counteract the effects of this extirpation.

Without going into detail I can say that experimental and clinical evidence with regard to dystrophia adiposo-genitalis, obesity, and other endocrine disturbances is equally unequivocal.

With this evidence before us we are forced to conclude that the symptoms under consideration may be caused by a purely nervous or a purely glandular lesion, and that the pituitary body and the nucleus hypophyseus and adjacent centres in the 'tween-brain work together as an endocrine-nervous system.

I submit that narcolepsy is another expression of disorder in this system.

Sleep attacks indistinguishable from those of idiopathic narcolepsy may occur with obesity, pregnancy and strictly localized pituitary disease on the one hand, while "pituitary signs" are common in idiopathic narcolepsy and were present in two cases where the symptoms of true narcolepsy followed encephalitis lethargica. In symptomatic narcolepsy, I surmise, the primary disturbance is in the gland; in idiopathic and post-encephalitic narcolepsy the nucleus hypophyseus and adjoining centres are at fault. It is not without significance that cataplexy occurs in narcolepsy of nervous origin only.

How this system influences sleep I do not know. Its constitution enables it to alter the nutrition of the whole organism; perhaps the nutrition of the nervous system is so altered throughout that the spread of inhibition is favoured wherever it arises; perhaps it influences structures in its immediate neighbourhood only, in such a way that inhibitions arise more readily and spread more easily to modify the activity of normal structures at a distance. If it had to be one or the other I should favour the second alternative, but the evidence I shall now give convinces me that it acts in both ways.

I have attempted to prove that sleep in narcolepsy is true sleep, that sleep and cataplexy on emotion are inhibitions, and that these are exaggerations or slight perversions of normal phenomena, but I have not yet considered why certain individuals present these symptoms.

Now Pavlov found that the tendency for inhibition to spread and produce sleep was much greater in some animals than in others; lively animals with a labile nervous system slept readily, while quiet, easy-going animals rarely slept. By studying the general nervous

character of the animals it was possible to foretell whether they would become sleepy during the experiments. The explanation is that in animals lively when running free the constant displacement of inhibition by new and varied excitations prevented sleep; in the experimental stall stimuli were few and monotonous, inhibitions spread unchecked and the animals slept. The quiet animals with a more stable nervous system did not need so many stimuli to prevent the spread of inhibitions and sleep did not occur so readily; the tendency to sleep varies with the general nervous character of the individual. Again, during the "bad years" in Russia (1919-20), when the dogs were underfed and therefore easily fatigued, sleep occurred so readily that the experiments on conditioned reflexes had to be abandoned; in several cases of narcolepsy the attacks came on for the first time after physical exhaustion or prolonged deprivation of sleep; further, in almost every case of narcolepsy rest produced very definite amelioration or even temporary cure, with a return of symptoms when ordinary life was resumed. This shows that inhibitions spread more readily in a fatigued brain.

The type of nervous activity in an individual is a general character, likewise his sleep habits, and his response to emotion, physical exhaustion and deprivation of sleep. It seems then as if narcolepsy is an expression of fatigue in individuals with a kind of nervous activity that favours the spread of inhibitions and allows excessive emotional responses; further, that the local response to inhibitions, wherever they arise, is abnormal, and that the symptoms are due to a general alteration of nervous activity rather than to abnormal stimuli which affect normal structures at a distance. This conception of narcolepsy is not inconsistent with existing knowledge, for an analogous disorder in another endocrine-nervous system, Graves's disease, presents comparable features. In this system too a ductless gland and sympathetic centres in the brain-stem are in intimate physiological connection.

From my own observations on Graves's disease I am convinced that just as sleep attacks may occur with disease of the pituitary body or in the 'tween-brain, so may some of the symptoms of hyperthyroidism be caused by disease in the brain-stem or in the thyroid gland itself. Indeed my impression is that the nervous portion of this system is primarily the more important. Of Graves's disease what I have said of narcolepsy—that the nutrition of the whole organism is altered—will be readily admitted; also that one of the expressions of this altered nutrition in nervous structures is an excessive response to emotional and other stimuli. But I do not say that these responses result from

the discharge of abnormal stimuli from the optic thalamus or from centres in the mid-brain, nor do I find it necessary to postulate the existence of special centres to account for them. The emotional state, the restlessness, and the heightened metabolic activity in Graves's disease contrast with the stodginess, the obesity, the excessive night sleep, the difficulty in waking in the morning and the constant sleepiness during the day that are common in narcolepsy; clinically they are corresponding opposites; the endocrine-nervous mechanism in both is strictly analogous; hence the nervous symptoms in both may well be due to a general rather than a local perversion of nervous activity.

All this notwithstanding, there can be little doubt that the cardinal symptoms in true narcolepsy result in the end from a direct spread of inhibitory impulses from subcortical centres along nervous paths. We have seen that cataplexy on emotion often passes into sleep; considering the close anatomical relations of the parts concerned in the regulation of muscle tone and the motor, vasomotor and other vegetative reactions on emotion to the part in which I have placed the lesion causing sleep in narcolepsy, these transitions are most easily explained by assuming that inhibitions arising in one group of structures may spread to affect the other. The thalamus, the corpus striatum, the substantia nigra and the red nucleus are all in the immediate neighbourhood; they all form a part of the complicated mechanism subserving muscle tone, and the thalamus certainly forms a part of the mechanism concerned in reactions to emotion. The inevitableness of sleep and its sudden, sometimes lightning-like, onset in narcolepsy also suggest that subcortical centres inhibit cortical activity and that the impulses travel by direct nervous paths. In a normal person a sudden feeling of sleepiness may be dispelled by an effort of the will, by voluntary excitation of the cortex, but in narcolepsy sleep is inevitable once the inclination is felt—subcortical centres prevail over the cortex.

Further evidence that subcortical centres may influence cortical activity is provided by certain sequels of encephalitis lethargica. Victims of this disease often show psychical defects of a kind and intensity that we associate with severe psychoses or hysteria—catalepsy, catatonic stupor or extreme mental apathy and lack of spontaneity, alteration in character, imperative utterances, various respiratory and other motor tics and the like. These may be explained by assuming that the cortex is affected in these cases; but it is more probable, as Economo believes, that these symptoms are due to an organic subcortical lesion; if this is true we must conclude that part of the complex

function we call volition is not only outside consciousness but entirely extrapsychical. A part of volition may indeed be independent of cortical activity, or perhaps subcortical lesions alter the nutrition of the cortex and so produce their effects indirectly; whatever the true explanation is, it is certain that psychical processes may be influenced by a purely subcortical lesion.

Narcolepsy and Subcortical Sleep Centres.

I shall now consider the bearing of my findings in narcolepsy on the mechanism of normal sleep.

Pavlov and his pupils have crystallized their conception in the words "sleep and internal inhibition—one and the same process." Now the processes studied by Pavlov are cortical, and his cortical mechanism seems sufficient to explain the phenomena of normal sleep.

It is difficult to believe that the fine adaptations in conditioned and differential inhibition could take place outside the cortex. These were complicated by sleep; sleep may pass into inhibition or inhibition into sleep; sleep may be replaced by inhibition or there may be a summation of sleep and inhibition. The two things are so closely bound up the one with the other that it seems unreasonable to deny that they are one and the same process; if they are, then the mechanism for sleep too must be in the cortex. Again, the purpose of sleep is to provide rest; the part of the body for which rest is essential is the central nervous system; the part of the central nervous system which requires it most is surely the cerebral cortex; reason dictates that the structure that requires rest must provide for itself. Nevertheless, the prevailing notion is that sleep is initiated and controlled by subcortical "sleep centres." The important hypotheses in this connection are those of Trömner and of Economo.

Trömner in his book, "Das Problem des Schlafes" (1912), reviewed theories of sleep then existing only to condemn them and formulated the hypothesis which he has recently defended that sleep is regulated from a centre in the optic thalamus. His argument is somewhat as follows: Sleep results from a sudden complete interruption of sensory impressions (Sinnesblockade) on their way to the cortex; an organ must exist capable of producing this sudden blockade; by virtue of its connection with all the senses and all parts of the cortex the optic thalamus has this power; sleep is initiated in and controlled by one organ—the optic thalamus.

According to this simple hypothesis we sleep or wake under thalamic

control, as a room may be plunged into darkness or flooded with light by the movement of an electric switch. In normal sleep centripetal impulses are interrupted, and by virtue of its control over other subcortical centres tone in the muscles is diminished and automatic movements cease; if centripetal impulses alone are interrupted tone persists, and automatic movements are possible, so that the somnambulist may walk though fast asleep; if centrifugal stimuli alone are impeded tone may be lost, so that the muscles are useless though consciousness is retained.

There is considerable evidence for the belief that the thalamus forms an important part of the complicated mechanism concerned in the motor and vegetative reactions of the organism to emotion, and I assume for the sake of this argument what some accept as proven, that the thalamus plays a part in the control of muscle tone.

In narcolepsy then, we might say, a sudden emotional stimulus causes loss of tone and sleep according to the upward or downward spread of impulses from the thalamus. But many arguments may be adduced against Trömner's convenient hypothesis. We must depend in part at least for our knowledge of the mechanism of sleep upon investigations on diseases with excessive or untimely sleep as symptoms.

Isolated lesions of the thalamus, so far as I know, never cause disorders of sleep. Trömner considers that cases reported by Hirsch [10] and by Pette [21] support his contentions. In Hirsch's case "an abscess as big as a hen's egg" was found in a patient who slept excessively during the last days of his illness, but the late onset of excessive sleep might well be used as an argument against Trömner's view. Pette used his case to support a rival hypothesis; in other cases extrathalamic lesions, namely tumours, are supposed to have produced excessive sleep by pressure on the thalamus, but they are valueless as evidence.

In diseases with disorder of sleep there is, as a rule, no objective sign whatsoever of interruption of sensory impulses from the periphery, nor is excessive or untimely sleep a symptom of thalamic lesions with gross objective sensory disturbances.

My conclusion then is that the thalamus is eminently fitted by its anatomical connections with the cortex and subcortical structures to exert an influence upon the cortical sleep mechanism and upon muscle tone; that no other single structure is so favourably situated; that the thalamus very probably forms an important *part* of the nervous mechanism of sleep, and of the nervous mechanism that is disordered

in narcolepsy; but that its effects, if any, are produced not by interruption of ordinary sensory impulses but by a setting in motion of some inhibitory mechanism whose nature is at present unknown. Trömner's hypothesis that sleep is initiated and controlled by the optic thalamus *alone*, however, cannot be upheld, for Pavlov has shown that sleep *can* arise in the cortex, and the evidence I shall now give proves that an important part of the sleep mechanism is situated in the mid-brain and 'tween-brain.

In 1890 Mauthner [15] took part in a discussion on "a curious and deadly sleeping sickness" then called nona, and foretold that the lesions causing sleep in this disease would be found in the grey matter surrounding the aqueduct of Sylvius; he had not seen a case of nona (now known as encephalitis lethargica) but based his prediction on his knowledge of pathological conditions in which ocular palsies and excessive sleep are cardinal symptoms; this combination is seen, for example, in Wernicke's polio-encephalitis hæmorrhagica, in Gerlier's "vertige paralysant," in Gayet's "disease," and with tumours and other morbid processes that damage the walls of the third ventricle and adjacent parts. Diseases affecting these parts were rare until recent years, but the association of ocular palsies with disorders of sleep is now familiar. Knowledge gained from a study of the lesions in encephalitis lethargica caused Economo [3] to follow Mauthner and place the lesion causing disturbances of sleep in this disease in the grey matter of the mid-brain.

Many of those, however, who write on sleep centres in the central grey matter quote Economo's words out of their context, and thus attribute to this careful writer a statement which is narrow in its implications and does scant justice to his broad views on sleep. In his memorable article on encephalitis lethargica his words are somewhat as follows: "The fact that sleep is disturbed in three ways—excessive sleep, sleeplessness and reversal of the sleep rhythm—leaves room for no other conclusion than that encephalitis is primarily responsible for these disturbances. The great apparatus that controls periodic sleep is nervous in part only; some of the most important links in the nervous chain lie in the 'tween-brain and mid-brain, especially in the posterior wall of the third ventricle and in the adjoining grey matter of the interpeduncular region, the aqueduct and the tegmentum. How this region regulates sleep we do not know; it may be by altering the cerebral blood supply; it may be that it influences the sum of cerebral functions concerned in consciousness (Bewusstseinsgesamtfunktionen

des Grosshirns); or it may be that hormonal influences activated or inhibited by these centres produce effects upon the whole body including the hemispheres. In any case it must be accepted as a physiological fact that a centre exists here from which sleep may be influenced primarily; the fact that other important vegetative functions of the organism are also under the influence of this region makes our conception very plausible."

It will be seen from this quotation that Economo does not say that normal sleep is initiated in subcortical centres and regulated primarily by them alone; out of their context the words "how sleep is regulated from this region we do not know at present" (Worin die Regulation des Schlafes von hier aus besteht ist vorderhand nicht lösbar) might suggest that he holds this view; but if I understand him aright his contention is that *some* of the most important links in the chain of structures concerned in sleep are situated there and that the parts he names *can* influence sleep primarily. The narrower view of many who profess to follow Economo is illustrated in the conclusions of Pette, who recorded the case of a man who lay for three months, from the acute onset of his illness to his death, in a state which "resembled in a remarkable manner the lethargic condition seen in encephalitis lethargica, so that the presence of this disease was considered to be highly probable." After death an area of softening was found "in the tegmentum between the substantia nigra and the aqueduct." Pette concludes that "there exists in the grey matter in the floor of the third ventricle a point which has an important connection with the function of sleep; probably it is *the* sleep centre itself."

Luksch [13] described a case of infective endocarditis in a man who slept almost continuously during the fortnight before his death; an embolic abscess was found "in the grey matter of the caudal part of the third ventricle and in the wall and surrounding parts of the beginning of the aqueduct." These cases are important because the lesions are circumscribed; they support the notion that it is lesions in these parts that produce sleep in encephalitis lethargica—a diffuse disease. But the area named by Economo is comparatively large. I believe that the facts in narcolepsy and in other conditions in which excessive or untimely sleep occurs without ocular palsies give the clue to a more precise localization of the subcortical centres concerned in sleep.

We have seen that attacks of sleep of sudden onset occur with pituitary disease and in conditions such as pregnancy where alterations occur in the pituitary body. In these cases and in true narcolepsy

there are no ocular symptoms apart from those of normal sleep. In my case of narcolepsy after encephalitis lethargica there were no residual ocular signs; in Stiefler's case likewise, apart from slightly defective contraction of the pupils on convergence of the eyeballs, there were no ocular signs of the primary disease.

The combination of ocular palsies with excessive sleep then is good evidence of a lesion somewhere within the area named by Economo; but it is only a rough guide to the parts that are responsible for sleep. The evidence from the conditions I have named seems to me to indicate that the part we are seeking is in the floor of the 'tween-brain in and around the vegetative centres that form a part of the pituitary 'tween-brain system. These centres, which are perhaps purely vegetative, certainly influence sleep primarily in functional and organic diseases, e.g., in narcolepsy and encephalitis lethargica; it is reasonable to infer, therefore, that they play a part in normal periodic sleep. If they do we may speak with propriety of corticogenic sleep as described by Pavlov, and subcorticogenic sleep. How subcortical centres influence sleep we do not know, but as periodic sleep is essentially a part of the vegetative life of the organism it is almost certain that harmones play a part; here again, as in narcolepsy, it is possible that sleep may be turned on and off, as it were, by inhibitions that arise in subcortical centres and influence structures at a distance along direct nervous paths.

In so far then as sleep is certainly influenced primarily from subcortical centres in some way entirely unknown, we are justified in saying loosely that *a* sleep centre exists in the region I have named, but we should speak of it as *the* sleep centre with reserve lest we forget that the sleep problem is not thus solved, and that complicated biological processes such as sleep are not controlled by single centres but by the balanced action of many nervous and endocrine nervous mechanisms working in unison.

We do well to remind ourselves too of the changes in doctrine that have occurred from time to time concerning the manner in which the organs of the body work together. The rapid increase of knowledge that came with discoveries on the anatomy and physiology of the nervous system led to the notion of purely nervous connections and displaced existing humoral theories. Another remarkable series of discoveries in connection with the ductless glands then led to over-emphasis of a humoral theory in another form. My study of narcolepsy has taught me that here again it is not a matter of either—or that nervous and endocrine organs work together as equivalent parts of an intimate

system; thus nervous centres may exert their influence through a ductless gland or a gland may act by stimulating a nervous centre (Schiff). The facts in symptomatic narcolepsy where the primary disturbance is in the pituitary body, and in idiopathic narcolepsy where the nucleus hypophyseus and adjacent centres are primarily at fault, provide a striking example of this endocrine-nervous correlation.

Summary.—The Facts.

In 1880 Gelineau described the first case to which the name narcolepsy was applied; he maintained that he had discovered a new form of neurosis distinct from epilepsy.

Thereafter until the present time the word had been applied indiscriminately to excessive or untimely sleep in many dissimilar conditions.

I record here twenty cases that conform to Gelineau's description, five of which have come under my own observation; accounts of about thirty cases not included here have been published.

The disease is characterized by the occurrence in the same patient at different times of two kinds of sudden attack; in one the patient is overcome without cause by an irresistible inclination to sleep; in the other, as the result of some emotional disturbance, the muscles become limp and powerless, consciousness being retained. Occasionally an attack following emotion ends in sleep; rarely attacks similar to those on emotion occur without cause; many attacks are transitional from one form to the other. Both sexes are affected; hitherto all the published cases were males; I record here two characteristic female cases.

The disease begins most frequently in adolescence, or in early adult life and rarely later than the fortieth year; apart from the presence of signs suggestive of pituitary disorder in many of the cases, the individuals affected appear to be healthy.

The frequency of the sleep attacks varies from two or three a day to one every few minutes, but is fairly constant in each individual; the duration of the attack varies from a few seconds to several hours, several minutes being most frequent. The depth varies from a light sleep in which the patient is dimly aware of his surroundings and can be wakened by a light touch or a call, to profound sleep from which he is wakened with difficulty.

Sleep may occur in any circumstances whatsoever and may endanger life; the attack is almost always inevitable; the condition in the attack coincides in every particular with that of normal sleep.

Any emotion, pleasurable or the reverse, may precipitate the second kind of attack; hearty laughter is the most potent cause; some patients can laugh with impunity but have an attack with other emotions; patients sometimes learn to check the inclination to laugh and can thus prevent the attacks.

Most of the symptoms in an attack on emotion can be attributed to sudden loss of tone in the muscles, but grimacing, protrusion of the tongue, stammering, twitching of the lids, and jerky movements of the head or limbs may occur, and the patient may be unable to move or speak though fully conscious.

Patients with narcolepsy have been under skilled observation for periods extending up to twenty-one years; no patient with true narcolepsy has become epileptic or developed signs of any organic disease to which the attacks could be attributed.

Rest relieves the symptoms; no other form of treatment influences them favourably; complete and permanent recovery has not been observed.

Sleep attacks indistinguishable from those of true narcolepsy occur in many diseases, but (apart from the two cases mentioned here of narcolepsy after encephalitis lethargica) the combination of sleep attacks with attacks on emotion occurs in no other condition whatsoever.

Conclusions.

Gelineau's narcolepsy is a disease *sui generis*.

It is not very rare; most of the cases are mistaken for epilepsy, some for hysteria; it is certainly distinct from both.

The disease is of considerable medical, military and medicological importance.

The name narcolepsy should be reserved for the idiopathic disease; it should not be applied to excessive or untimely sleep when this is a symptom of some other disease; confusion would be avoided by using the terms idiopathic and symptomatic narcolepsy.

Other names that have been proposed for the disease have nothing to recommend them; the name narcolepsy should be retained.

The "short narcoleptic attacks" of Friedmann are distinct from the narcolepsy of Gelineau, and as they were described later they should bear another name; the name pyknolepsy is suitable for them.

The sleep in narcolepsy is indistinguishable from normal sleep. The attacks on emotion, in spite of contrary opinions, are highly

characteristic of the disease. The terms cataplexy and cataplectic are suitable for them. Sleep and cataplectic attacks, though apparently different in nature, are essentially the same: both result from sudden inhibition.

Pavlov's conception of the nature of normal sleep receives confirmation from this study of narcolepsy. The symptoms in narcolepsy become comprehensible in the light of Pavlov's researches.

Sleep and cataplexy may follow encephalitis lethargica and produce a condition indistinguishable from true narcolepsy: these cases tend to recover, but true narcolepsy persists throughout life.

True narcolepsy is a functional disorder of the nervous system, probably an undue fatigability of nerve cells, in individuals with a peculiar kind of nervous activity that allows excessive responses to emotional stimuli and favours the spread of inhibitions.

The pituitary body with the nucleus hypophyseus and adjacent vegetative centres in the floor of the 'tween-brain forms an endocrine-nervous system; diabetes insipidus, dystrophia adiposo-genitalis and other endocrine disorders may arise from disease confined to the gland or the 'tween-brain: narcolepsy is primarily a disorder of this system.

Sleep may arise in the cortex or in subcortical centres: in narcolepsy and in diseases where excessive sleep and ocular palsies are cardinal symptoms the site of the lesion causing sleep is in and around vegetative centres in the 'tween-brain. This subcortical centre can influence sleep primarily, but it is only a part of the mechanism of normal periodic sleep, which in its turn is only in part nervous; it should not be referred to as *the* sleep centre.

REFERENCES.

[1] CURSCHMANN and PRANGE. *Deutsch. Zeitschr. f. Nervenheilk.*, 1925, **86**, 97.
[2] DERCUM. *Journ. of Nerv. Diseases*, 1923, **40**, 185.
[3] ECONOMO, C. *Wien. med. Wochenschr.*, 1923, **73**, 777.
[4] FISCHER. *Arch. f. Psych. u. Nervenkrankh.*, 1878, **8**, 20.
[5] FRIEDMANN. *Deutsch. Zeitschr. f. Nervenheilk.*, 1906, **30**, 462.
[6] GELINEAU. *Gaz. des Hôp.*, 1880, **53**, 626.
[7] GOLDFLAM. *Deutsch. Zeitschr. f. Nervenheilk.*, 1924, **77**, 20.
[8] HANN. *Frankf. Zeitschr. f. Path.*, 1918, **21**, 337.
[9] HENNEBERG. *Neurol. Centralbl.*, 1916, **35**, 282.
[10] HIRSCH. *Med. Klin.*, 1924, **20**, 1324.
[11] JOLLY. *Deutsch. Zeitschr. f. Nervenheilk.*, 1916, **45**, 236.
[12] KOLLEWIJN. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.* (Ref.), 1923, **31**, 352.
[13] LUKSCH. *Ibid.* (Orig.), 1924, **93**, 83.
[14] LÖWENFELD. *Münch. med. Wochenschr.*, 1902, **80**, 1041.
[15] MAUTHNER, L. *Wien. klin. Wochenschr.*, 1890, **3**, 445.
[16] MENDEL, K. *Neurol. Centralbl.*, 1916, **35**, 359.

[17] NEVERMANN. *Deutsch. med. Wochenschr.*, 1921, **47,** 1164.
[18] NOACK. *Neurol. Centralbl.*, 1918, **37,** 27.
[19] OPPENHEIM. *Monatschr. f. Psych. u. Neurol.*, 1902, **11,** 241.
[20] PAVLOV, I. *Skand. Arch. f. Physiol.*, 1923, **44**, 32.
[21] PETTE, H. *Deutsch. Zeitschr. f. Nervenheilk.*, 1923, **56,** 236.
[22] PIERON, H. "Du Sommeil," Paris, 1913.
[23] PINES, I. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1925, **100,** 123.
[24] PINEY and COATES. *Journ. of Path. and Bact.*, 1924, **27,** 211.
[25] REDLICH, E. *Monatschr. f. Psych. u. Neur.*, 1915, **37,** 85.
[26] *Idem. Zeitschr. f. d. ges. Neur. u. Psych.*, 1925, **95**, 256.
[27] SCHIFF. *Wien. klin. Wochenschr.* (Sonderbeilage), **38,** 21.
[28] SIMMONDS. *Münch. med. Wochenschr.*, 1913, **60**, 137.
[29] *Idem. Verhandl. d. deutsch. Path. Gesellsch.*, 1914, 208.
[30] SINGER. *Zeitschr. f. d. ges. Neur. u. Psych.*, 1917, **36**, 278.
[31] SOMER. *Wien. klin. Wochenschr.*, 1921, **12**, 132.
[32] STIEFLER. *Neurol. Centralbl.*, 1918, **37**, 380.
[33] *Idem. Wien. klin. Wochenschr.*, 1924, **37**, 1044.
[34] STÖCKER. *Zeitschr. f. d. ges. Neur. u. Psych.*, 1913, **18,** 217.
[35] TRÖMNER, E. "Das Problem des Schlafes," Wiesbaden, 1912.
[36] WENDOVERIĈ. *Arch. f. Psychiatr.*, 1924, **72**, 459.
[37] WESTPHAL, C. *Arch. f. Psychiatr. u. Nervenkrankh.*, 1877, **7,** 631.

A CONTRIBUTION TO THE STUDY OF DEPOSITS CONTAINING CALCIUM AND IRON IN THE BRAIN.[1]

BY ELIZABETH COWPER EAVES, M.D., B.S., B.Sc.Lond.

Lecturer in Physiology, University of Sheffield.

(From the South Yorkshire Mental Hospital, Wadsley, Sheffield, and the Physiological Department, University of Sheffield.)

Calcified deposits and calcification of the blood-vessels in the central nervous system have been described at intervals by various observers. The former condition is usually considered to be rare. Opinions differ as to the relative frequency of the process in the blood-vessels. Thus, for instance, Obersteiner [17] remarks that it is of common occurrence; Byrom Bramwell [3] says that in his experience an advanced degree of calcification in the smaller vessels is unusual. This diversity of opinion is also shown by other writers.

The discovery within recent years of calcified deposits and blood-vessels in the central nervous system in epidemic encephalitis has renewed interest in the subject.

It is to be noted that not all observers who have recorded calcification in the brain in different conditions have definitely proved its existence. A staining reaction with a pure hæmatoxylin solution is sometimes taken to be sufficient evidence of the presence of calcium. This is not necessarily the case.

Reactions given by a Fresh Solution of pure Hematoxylin with Different Salts.

A freshly prepared solution of the pure substance has very little staining properties on normal tissues. From the chemical standpoint hæmatoxylin behaves like a weak acid. With calcium hydrate a blue precipitate is formed. This reaction can be applied as a microchemical test, but it is not in any way a specific reaction for calcium.

A fresh hæmatoxylin solution added to solutions or suspensions of different salts gave the following results:—

[1] A paper by E. W. Hurst, on "Calcification in the Basal Ganglia," was published in January, 1926, after the substance of this paper had been communicated to the Sheffield Medico-Chirurgical Society (December 10, 1925), and most of it was written. Points in which the results here published agree or disagree with the conclusions in that paper are referred to in the following pages.

Calcium phosphate, purplish red insoluble compound.
Calcium soaps, purple insoluble compound.
Calcium sulphate and calcium chloride, red colour.
Caustic soda 0·1 per cent., red colour.
Caustic soda 8 per cent., deep blue colour.
Magnesium sulphate, red colour.
Magnesium oxide, intense blue insoluble compound.
Ferric chloride, black precipitate.
Ferrous sulphate, blue colour.
Ferrous sulphate mixed with ferric salts in certain proportions, blue precipitate.

The addition of a weak acid, such as phosphoric acid, destroyed the colour in all the above cases.

In microchemical reactions salts of iron and magnesium are more likely to cause difficulty in testing for calcium than those of the alkalies, as the latter form soluble compounds with hæmatoxylin.

For iron there are of course characteristic colour reactions (Prussian blue and ammonium sulphide reactions). It is obviously necessary to exclude iron before assuming that a blue staining with hæmatoxylin signifies calcium.

Furthermore, it is conceivable that salts of calcium in the nervous system may not give this reaction in certain circumstances. It seems a possibility that in the disintegration of nervous tissues there is formed phosphoric acid, the presence of which could prevent any interaction between calcium salts and hæmatoxylin.

It will be shown later that abnormal tissue may stain with hæmatoxylin even in the absence of any inorganic salts.

The production of a precipitate of calcium oxalate, insoluble in acetic acid, is a characteristic and a very sensitive test for calcium from the chemical standpoint, but as the precipitate is colourless the reaction cannot be applied microchemically. A quantitative analysis of the nervous tissue is often the only method of detection of an increased amount of calcium.

Where the amount of deposit is very large (as in Cases 1 and 2 described here), extraction of a small portion, about two or three grammes of brain, with acetic acid, will suffice for the demonstration of calcium in the solution. This method can rarely be used.

Iron in the Nervous System.

Iron, in a form stainable by the inorganic tests for this substance, has been shown to occur in certain situations in the normal nervous

system except in the fœtus, and in the first few months of life. This was first described by Guizzetti [12] in 1915, and recently corroborated by Spatz [19], and Gans [10]. The globus pallidus gives an intense reaction, the putamen and caudate nucleus a weaker one, the cerebral cortex only a very slight reaction. Gans states that the reaction is not given at all if the material has been kept in formalin longer than three days.

In all the cases recorded in this paper the material had been in formalin for some time, so that where the reaction is obtained it cannot be a question of " physiological " iron—which is evidently easily soluble—but of some much less soluble compound.

Two Cases of Angiomata of the Brain with Calcified Deposits, and Calcification of the Vessels.

The two cases to be described afforded a somewhat unusual opportunity of studying the chemical nature of the deposit owing to the extent of the process.

Case 1 is of especial interest as the patient had a nævus of the face, a similar condition affecting the cerebral hemisphere of the same side, and an extreme degree of calcification of part of the cerebral cortex. Clinically, signs suggestive of hypopituitarism were present.

Case 1.—A girl, aged 16 (a patient of Dr. Gillespie), suffered from epileptic fits almost from birth, and certainly from the age of 9 months epilepsy was well established. She was always very backward even when a baby. She was admitted at the age of 15 to the South Yorkshire Mental Hospital, in June, 1924. She was then mentally defective, being unable to follow what was said to her, and very slow in framing any reply. Her vocabulary was very limited. She had at this time and until her death many attacks of *petit mal* in a day. These were almost too numerous to count. She also had many severe major attacks of epilepsy.

Early in March, 1925, she began to complain very much of headache and looked ill. The following notes about the case from this time are given by Dr. Gillespie :—

March 16: Complains of headache, temperature 102° F.

March 18: Chest examination, prolonged expiration at both bases. Tubercle suspected.

March 22: Headache continues. No retraction. Kernig's sign absent.

March 23: Much feebler; morning and evening rise of temperature. No physical signs indicative of meningitis. Complains still of headache.

The patient died on March 25, the cause of death being acute general miliary tuberculosis.

Condition.—Height, 4 ft. 7 in. Weight, 5 st.

She was undersized and underdeveloped for her age, otherwise the only anatomical feature worthy of note was the tapering condition of the fingers. There was an extensive nævus on the right cheek and on the right side of the forehead.

Nervous system.—Nothing very abnormal was found. Touch and pain sense seemed to be diminished. The knee-jerks were difficult to elicit. Romberg's sign was absent. Nothing abnormal was observed in the eyes.

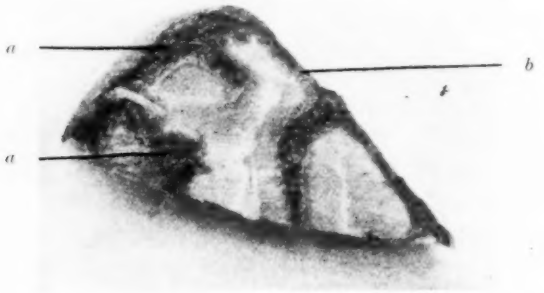


FIG. 1 (*Case* 1).—A portion of cerebral cortex; angiomatous pia mater and calcification in cortex. *a*, Angioma of pia mater. *b*, Gritty deposit in cortex. × 2½.

Circulatory system.—A systolic murmur at apex, conducted towards left axilla. Blood-pressure 95 mm. systolic (shortly after a fit), measured on several other occasions 85 to 90 mm. systolic.

Respiratory system.—Nothing abnormal on admission (in June 1924).

Post-mortem examination.—Almost all the organs contained miliary tubercle.

The pituitary, which weighed 0·5 grm., was more deeply embedded in the sella turcica than is usual, and there was some increase of the posterior clinoid processes. The thyroid weighed only 11 grm. As both pituitary and thyroid contained miliary tubercle, any detailed examination of their histological structure seemed useless. Microscopically when cut across the ovary showed no Graafian follicles.

The brain weighed 37 oz. It was asymmetrical, the right hemisphere being very much smaller than the left. There was no disproportion in the case of the lobes of the cerebellum.

On the surface of the right hemisphere there was an angioma of the pia mater in the frontal region, extending to and implicating the leg area of the motor cortex. There was a similar condition in the right parieto-occipital region. The angiomata were not circumscribed. The left hemisphere showed no outward sign of any similar condition.

On making a section of the brain in the occipital region, where the angiomatous condition of the pia mater was pronounced, some degree of resistance to the knife was experienced. This was due to the existence of a gritty deposit in the cortex, which was translucent in appearance and is faintly indicated in the photograph of this piece of the brain (fig. 1). The freshly cut surface of the brain was free from blood-staining or hæmorrhage.

For microscopical examination frozen sections were mainly used. Some difficulty was experienced in obtaining good sections owing to the hardness of the deposit.

The following methods were applied to sections of the brain in this case, and in most of the others recorded in this paper:—

(1) Examination of unstained sections for the presence of pigment.

(2) Staining sections with a pure freshly made hæmatoxylin solution.

(3) Staining sections for fat with Scharlach R. and osmic acid.

(4) Test for phosphates. Sections were immersed in silver nitrate (10 per cent. solution) for about three minutes. Inorganic phosphate gives a yellow precipitate almost immediately. This blackens readily either on exposure to light or by treatment with formalin. (Carbonates and chlorides give a white precipitate which can be darkened in the same way.) The presence of phosphate was confirmed by the formation of yellow phosphomolybdate with ammonium molybdate in the presence of nitric acid.

(5) Sections were treated with potassium ferrocyanide (3 per cent.) and then placed for three to five minutes in 1 per cent. nitric acid (Prussian blue reaction for iron). This reaction is given by inorganic iron salts and also by hæmosiderin. In the former case the reactions take place rapidly (e.g., after about five minutes in ferrocyanide). Where the iron is present in a pigment, such as hæmosiderin, a much longer time in the ferrocyanide solution is necessary (at least twenty minutes). The reagents used were tested previously for the presence of iron as an impurity.

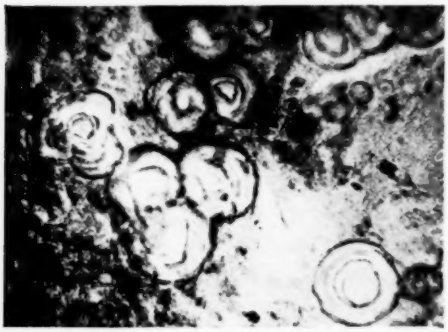


FIG. 2.—Cerebral cortex stained by Scharlach R. Concentric bodies similar to so-called "psammoma" bodies unstained. Fatty material edging these structures and free in the tissues outside. (Originally × 500, but reduced in illustration to two-thirds former size.)

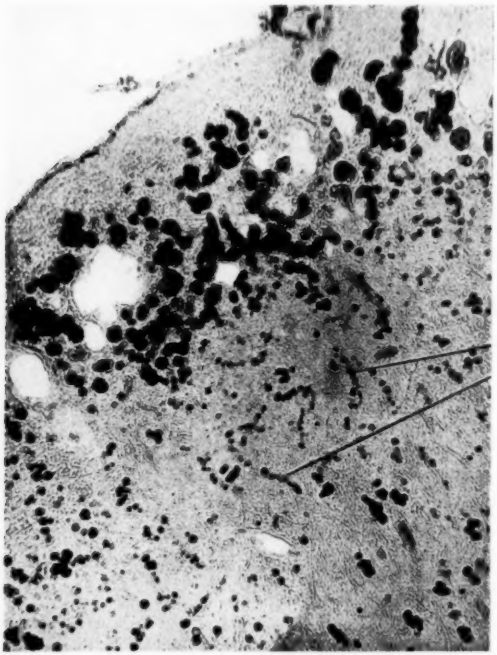


FIG. 3.—Cerebral cortex from calcified area. Frozen section. Stained by hæmatoxylin solution. Globules of gritty material are seen, the larger masses being situated near the surface of the cortex. The calcified material has fallen out in some places, leaving clear spaces. *a*, Deposit of granules along capillaries. × 40.

(6) Sections were treated with hot acetic acid. Calcium salts, such as carbonate phosphate, are readily soluble. Iron salts (carbonates, phosphates) are completely insoluble. After acetic acid sections were treated as in (2) (4).

(7) Stain for neuroglia by methyl violet preceded by Anderson's mordant. (Victoria blue is used in Anderson's modification of Anglade's method for neuroglia. The present writer prefers methyl violet, the method being, however, essentially the same.)

(8) Pyronin methyl green; modification of the Unna-Pappenheim method.

Examination of microscopic sections showed the presence of varying size masses in the cortex similar in appearance to the so-called "psammoma bodies." The concentric structure of many of these bodies was seen best in unstained or faintly stained preparations (fig. 2). They were not observed to contain any pigment.

The capillaries seemed abnormally numerous in the deeper parts of the cortex.

In hæmatoxylin-treated preparations the large globules stained in different shades of red and purple, the smaller and less superficial globules black and a bluish black. Along very many of the capillary vessels were numerous small granules about the size of a micrococcus (fig. 3). Some of the larger vessels were converted into solid cylinders.

Preparations stained by Scharlach R. and osmic acid showed that although there were numerous fat-granules free in the tissue very few of the globular deposits gave any reaction for fat. When present the staining was either very slight or the fat was visible as fine granules, being apparently an inclusion in the concentric bodies rather than comprising a definite part of the mass.

An intense reaction was given by all the deposit for inorganic phosphates (fig. 4).

The Prussian blue reaction showed that many of the globules contained iron. In the more superficial part of the cortex the reaction varied in intensity, some of the globules being a very dense blue. The granules along many of the capillary walls gave a marked iron reaction, and indeed in some areas served to outline the vessels in an unstained preparation treated by the Prussian blue reaction (fig. 5).

Sections boiled in acetic acid showed that a large amount of phosphate had been thus dissolved. Some of the masses still gave an intense phosphate reaction. The Prussian blue reaction for iron appeared the same as before treatment with acetic acid. From this it

FIG. 4.—Cerebral cortex from calcified area. Section treated with silver nitrate reaction for phosphates. Deposit gives an intense reaction, both in the more superficial concretions and in the granules outlining many of the capillary walls. The section is otherwise unstained. × 40.

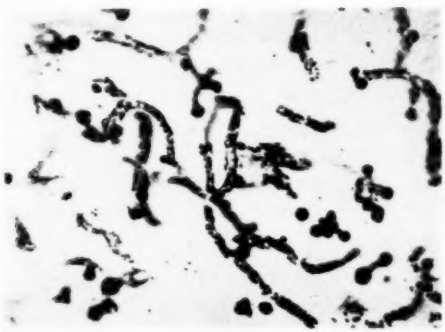


FIG. 5.—Prussian blue reaction for iron. Capillaries outlined by fine granules giving marked reaction for iron. Preparation otherwise unstained. × 280 in original photograph, but reduced to two-thirds of former size.

is to be inferred that only a small portion of the iron is present as a phosphate, the greater part being some other salt or compound of an insoluble nature.

Sections stained for neuroglia showed that there was an increase of fibres at the surface of the cortex, but not in the deeper parts. The nerve-cells were very much decreased in number.

It was to be presumed that the phosphate soluble in acetic acid was calcium phosphate, but in order to verify this the piece of brain containing the deposit was placed in 50 per cent. nitric acid for five days. Some effervescence occurred, showing the presence of carbonate. The nitric acid extract was tested for calcium (formation of a white precipitate with ammonium oxalate insoluble in acetic acid). This reaction was positive. The Prussian blue reaction was given faintly.

The decalcified block was embedded in the usual way in paraffin, the acid removed from the sections by alkali, the sections well washed and stained with pure hæmatoxylin solution. Many of the masses, except the larger ones, still stained with hæmatoxylin, the proportion of mineral deposit being evidently greater in the larger globules. The smaller and less superficial globules stained with hæmatoxylin in the same way as before decalcification. No reaction for iron was given, and as this is the least soluble of the constituents it is certain that other salts had been dissolved out completely also. It therefore seems that there was a groundwork of some organic substance in which mineral salts were deposited.

It seemed difficult to form an estimate of the relative importance of calcium and iron in the deposit by microchemical methods, as the Prussian blue reaction is a sensitive one, and can be given by traces of iron. An analysis of a portion of brain was therefore made.

Method.—A weighed portion of cerebral cortex (about 1 grm.) from the calcified area was heated to charring, a little ammonium nitrate solution added and the heating repeated until all organic matter had disappeared, shown by the weight of the ash remaining constant. The ash was grey in colour. Concentrated hot acetic acid was added, but a portion of the ash remained undissolved.

This insoluble portion—which was regarded as ferric phosphate—was filtered off, washed, dried and weighed. It dissolved readily in hydrochloric acid and gave the Prussian blue reaction.

The filtrate containing the calcium was made up to a stated volume, and aliquot portions treated with a saturated ammonium oxalate solution. The precipitate was washed, dissolved in sulphuric acid, and the

calcium estimated volumetrically with N/100 potassium permanganate solution. The filtrate after removal of calcium was found to contain a trace of sulphate.

Excess of ammonia was added to the filtrate. On long standing a small amount of crystals of ammonium magnesium phosphate separated (shown by the "knife rest" crystalline form under the microscope). This crystalline precipitate was filtered, washed, heated and weighed as magnesium pyrophosphate.

The amount of phosphorus in the greater part of the filtrate was estimated by precipitation with magnesium citrate in the presence of ammonia. The crystalline precipitate of ammonium magnesium phosphate was filtered, washed, heated and weighed as magnesium pyrophosphate.

Results of Analysis.

Amount of cerebral tissue used = 0·76 grm.

Amount of ash obtained = 0·065 grm.

This ash contained 0·016 grm. ferric phosphate and 0·015 grm. calcium phosphate. The magnesium present weighed only a fraction of a milligram, and the result therefore cannot be considered quantitative.

Amount of phosphate weighed as magnesium pyrophosphate = 0·022 grm. (This is less than the amount to be derived from the cerebral tissue used as some of the filtrate had been used for other tests before deciding to estimate the phosphate. Another source of loss lay in the fact that it seemed impossible to precipitate all the phosphate completely with magnesium citrate, the filtrate still giving a test for phosphates with ammonium molybdate.)

The following table gives the composition of the ash, compared with that from normal brain:—

	Cerebral cortex from Case 1 in region of calcified area. Percentage	Normal brain (maximum figures given by Geoghegan). Percentage
Total amount of ash..	8·55	.. 0·708
Iron calculated as $Fe_2(PO_4)_2$ ..	2·1	.. 0·0058
Calcium calculated as $Ca_3(PO_4)_2$ ..	1·95	
Calcium calculated as CaO ..	1·1	.. 0·0022
Phosphorus calculated as P_2O_5 ..	*1·87	.. 0·2

(* This figure is less than the amount present, as explained previously.)

A consideration of the above figures shows several interesting features. It will be seen that there is more phosphorus than can be accounted for by the amount necessary to combine with the increased

calcium. A possible explanation may be that the organic basis which has been demonstrated after removal of iron and calcium is a substance rich in phosphorus.

The calcium is present in amount five hundred times, the iron rather more than two hundred times, that in normal cerebral tissue. (There is the possibility that the figure for calcium may be too low as the material had been some months in formalin.)

Distribution of Deposit containing Calcium and Iron in the Brain.

It was most marked in the occipital cortex in the region in which the angiomatous condition of the pia mater was most pronounced.

The dentate nucleus of the cerebellum, the lenticular nucleus, optic thalamus and amygdaloid nucleus contained no trace of deposit, nor any abnormality of the vessels.

It is to be noted that although the base of the brain was affected by a tuberculous meningitic process there was no deposit in this region. The spinal cord also showed very considerable thickening of the meninges, but there was no deposit nor abnormality of the vessels.

Discussion of this Case.

A point of some interest, apart from the calcified deposit, is the association of a nævus of the face and brain with a strong possibility of dyspituitarism. The evidence in favour of the latter is the physical condition of the patient (resembling somewhat the Lorain type), the low blood-pressure and the anatomical condition of the posterior clinoid processes.

G. D. Head [14] has described a case of dyspituitarism associated with multiple hæmangiomas of the skin.

Dr. G. Holmes kindly showed to the writer one of his patients in the National Hospital, Queen Square, who exhibited Fröhlich's syndrome, and had multiple hæmangiomas of the skin.

Angiomata with considerable deposits of apparently calcified material have been recorded in a few instances, but the large amount of iron in these deposits has apparently not been suspected. Dürck [8] described a case of a diffuse racemose angioma of the pia mater with calcification of the cerebral vessels in a patient aged 19. Vanzetti [21], a similar case in a man aged 48, Oberndorfer [16], a cavernous angioma with extensive calcification of vessels and brain substance. The case given by C. F. Beadles [1] closely resembles this one.

Case 2.—A woman, aged 43 (patient of Dr. Gillespie).

There was unfortunately very little history obtainable.

During life the patient was regarded as being a case of an ordinary infantile hemiplegia due probably to old cerebral poliomyelitis. Epilepsy

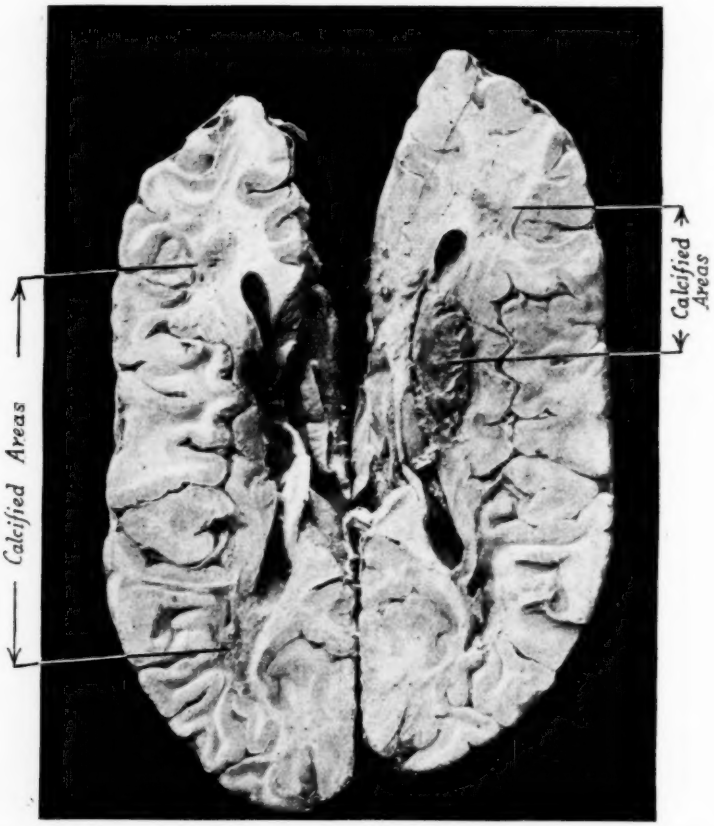


FIG. 6.—Right cerebral hemisphere, cut horizontally. Upper and lower parts of section.

began at the age of 22. The patient was admitted in September, 1922, to the South Yorkshire Mental Hospital at the age of 42, and was certified as an epileptic imbecile. She had frequent and severe epileptic fits.

She died about a year later, the cause of death being erysipelas and organic disease of the brain.

Condition of patient.—Height, 4 ft. 9 in. Weight, 5 st. 6 lb.

Circulatory system.—Nothing abnormal discovered. Arteriosclerosis was absent.

Respiratory system.—Nothing abnormal found.

Nervous system.—Left hemiplegia, the arm more affected than the leg and contractures present. The patient was only able to walk with a great deal of assistance. It was impossible to test sensation owing to the mental condition of the patient.

The post-mortem examination showed that all the organs were below normal weight. The brain weighed 35 oz. The ductless glands unfortunately were not saved. When the right hemisphere of the brain was cut across the corpus striatum appeared as a mass of almost stony consistency. Smaller and more diffuse areas of gritty material were present in the white matter in the frontal and parieto-occipital regions (fig. 6).

The left hemisphere showed the presence of a similar gritty material in the lateral part of the lenticular nucleus, and a small nodule in the part of the optic thalamus bordering the lateral ventricle.

A slightly pigmented gritty deposit was present in the dentate nuclei of both lobes of the cerebellum. A portion only of the right dentate nucleus contained this deposit, but in the case of the left nucleus no normal structure was visible to the naked eye, its whole situation being occupied by a circumscribed mass of gritty deposit.

The mid-brain showed no deposit macroscopically. In the upper part of the pons, about a centimetre anterior to the Sylvian aqueduct, the same gritty deposit occurred on the left side. This occupied approximately the situation of the fillet and affected some of the more dorsal pyramidal bundles. The condition was much more marked in the middle of the pons and diminished in the lower regions. The medulla, at the level of the olivary body and also in lower levels, contained no abnormal deposit—nor was any observed in the upper part of the spinal cord.

Corpus striatum.—Sections of the right corpus striatum were obtained with difficulty owing to the hard consistency of this structure. Examination of sections gave the impression that it was a question of an angiomatous condition, the structure resembling so markedly the appearance of the cortex in Case 1. Unstained sections showed the appearance of concretions, similar in appearance to the so-called "psammoma"-like bodies, and many vessels converted into solid cylinders. There was no ordinary nervous tissue present. There

was some neuroglia in places, but it had apparently mostly disappeared owing to the extent of the process. The majority of the concentric bodies gave no reaction at all with Scharlach R.

No pigment was present in the concretions, although some was present outside them. Many of the concentric structures and the solidified vessels gave the Prussian blue reaction for iron, and in some areas the capillaries were outlined by granules giving an iron reaction —the appearance being similar to that in Case 1 (fig. 5). The intensity of the Prussian blue reaction varied. The iron-containing

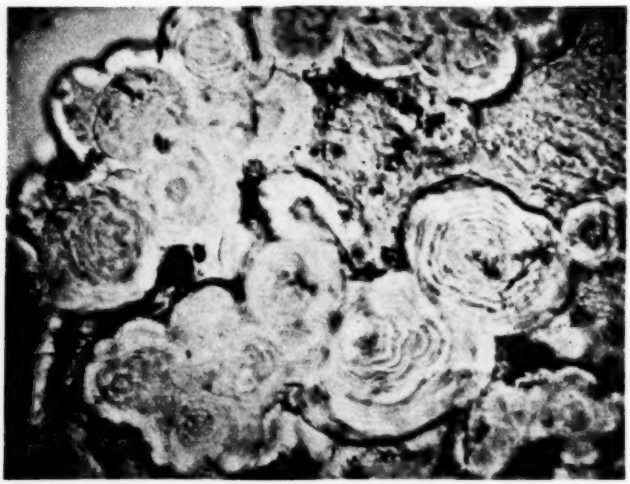


FIG. 7 (*Case* 2).—Corpus striatum containing deposit of concentric structures. The section was treated with Scharlach R., which assisted in outlining the concentric bodies, although they contained no fat except occasionally a few granules. There is some fatty material outside the concentric bodies. × 500.

concretions appeared to be limited to a part of the corpus striatum, an adjacent area of this structure containing similar gritty structures giving no Prussian blue reaction. The non-iron-containing structures exactly resembled in form the others which gave the Prussian blue reactions. In some instances a very massive concretion was tinged blue at the edge only by the ferrocyanide test. This was not due to failure of penetration of the solutions, as in the same area numerous very small globules, and also fine granules along the capillaries, gave no iron reaction at all. An intense reaction for phosphates was obtained, except in a few of the globules.

The dentate nuclei contained both iron and non-iron-containing concretions. In this region only a few of them gave an intense phosphate reaction.

Sections of the subcortical white matter in the right frontal lobe showed the same appearances as described in the corpus striatum and dentate nuclei.

No deposit was found microscopically in the cerebral cortex, midbrain, medulla, or spinal cord, but occasionally especially large or numerous vessels were observed.

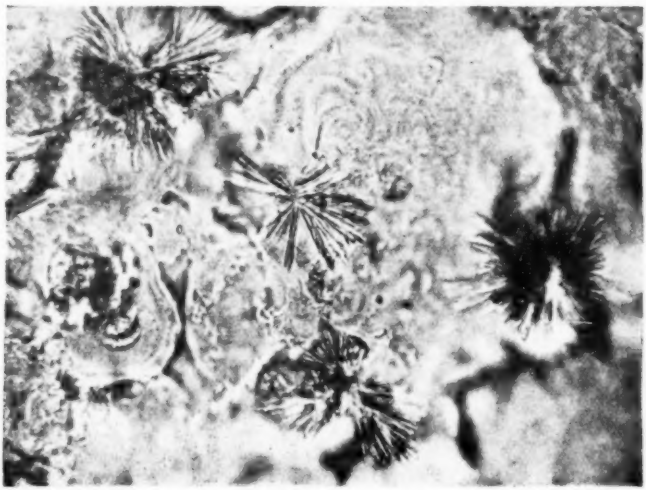


FIG. 8 (*Case* 2).—Section of deposit in subcortical white matter in frontal lobe. Section 25 μ in thickness containing deposit similar to that in fig. 7, treated with sulphuric acid and slightly stained with eosin. Five masses of gypsum crystals are shown, and the deposit is faintly visible in the background. × 500.

The middle of the pons contained a very hard deposit. Some of the concretions gave an iron reaction, but two or three exceptionally large ones gave no reaction. Many of the vessels were converted into apparently solid cylinders, and the capillaries were outlined by granules. While many of these gave a vivid iron reaction, in others the colour was faint or entirely absent. The phosphate reaction was very intense, but was not given by some of the solidified vessels and granules outlining the capillaries. The impression was obtained that some of the latter structures were deficient both in iron and phos-

phate, the absence of the latter indicating perhaps the absence of calcium, which appears to be very largely present as a phosphate.

Sections from all the different regions were boiled with acetic acid (in which calcium phosphate is soluble) and then tested for phosphates. In all cases it was obvious that a great deal of phosphate had been thus removed.

Chemical test for calcium.—About a third of a gramme of the corpus striatum was boiled with acetic acid, and the filtrate tested for calcium with ammonium oxalate. A precipitate of oxalate was readily obtained.

Quantitative analysis.—The left corpus striatum was analysed as the right one was so hard that it was difficult to obtain a small piece without spoiling the hemisphere as a specimen. About half a gramme was taken for the analysis. The material was ashed in the same way as described under Case 1, except that no ammonium nitrate was used to accelerate the ashing. After extracting the ash with acetic acid the clear filtrate was treated with ammonium oxalate. The precipitate of calcium oxalate being very abundant it was filtered off, washed, dried, heated and weighed as calcium oxide.

Weight of deposit used = 0·491 grm.

Weight of inorganic ash = 0·12 grm.

Weight of residue of ash insoluble in acetic acid (presumably ferric phosphate) = 0·043 grm.

Weight of calcium oxide = 0·0377 grm.

Calcified Corpus Striatum (*Case* 2).

	Calcified corpus striatum (Case 2). Percentage	Normal brain. Percentage (Geoghegan)
Amount of ash	24·43 ..	0·708
Iron calculated as $Fe_2(PO_4)_2$ ..	8·76 ..	0·0098
Calcium calculated as $Ca_3(PO_4)_2$ ..	14·1	
Calcium calculated as CaO	7·67 ..	0·0022

In different parts of the nervous system most of the nerve-cells exhibited the usual features that are found in severe epileptics, viz., chromatolysis and accumulation of fatty pigment. In the cerebral cortex there was an increase of neuroglial fibres, the latter forming a superficial felting. In other regions there was great neuroglial overgrowth in the regions where the deposit was present.

There was atrophy of the right half of the pons and degeneration of the pyramids. In the medulla the right pyramidal tract was atrophied

and degenerated. The left tract was not atrophied, but showed some slight degree of degeneration.

Discussion of Case 2.

As previously stated, this case is regarded as being one of multiple angiomata. From the clinical standpoint the condition during life was regarded as being a hemiplegia due to an old cerebral infantile paralysis, and indeed exactly resembled this disease. As frequently happens in the latter, the epilepsy was of a severe type and was accompanied by mental degeneration. Oppenheim [18] quotes a few cases resembling spastic infantile paralysis, in which angiomata of the brain occurred.

It is perhaps to be remarked on—in view of the morbid conditions of both corpora striata and both dentate nuclei—that no Parkinsonian condition was observed during life. The mid-brain, however, apart from the degenerated tracts, showed nothing unusual.

Epidemic Encephalitis.

Case 3 (patient of Dr. Mathieson).

A man, aged 52. He was admitted to the South Yorkshire Mental Hospital about two years before death, a provisional diagnosis of confusional insanity being made on admission. Some months later he was noticed to be apathetic and drowsy and began to develop a condition of Parkinsonism. A diagnosis of epidemic encephalitis was then made by Dr. Mathieson. Later the case was seen by Dr. Arthur Hall who confirmed the diagnosis. The Parkinsonian condition was extreme and the patient very wasted at the time of death from this disease, about eighteen months later.

The brain weighed 45 oz.

Frozen sections were examined. The cortex contained no deposit giving an iron or phosphate reaction, with the exception of one or two obvious minute hæmorrhages, which gave the Prussian blue reaction.

In the globus pallidus there were occasional small deposits giving a faint iron reaction. In the dentate nucleus of the cerebellum an intense reaction for iron was obtained in the walls of the fairly large vessels. This iron deposit was present in the tunica media, or in the intima and media.

A much more important deposit was found in the mid-brain. This was present a little distance away from the Sylvian aqueduct, and not far distant from the anterior corpora quadrigemina.

The deposit consisted of globules of various sizes, of one or two solidified vessels, and of two or three very large concretions. They contained no pigment. No reaction for fat was given with Scharlach R.

Many of the smaller and medium-sized globules gave a reaction for

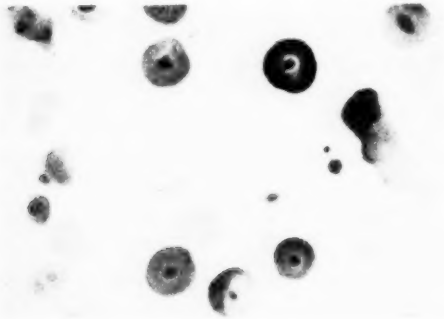


FIG. 9 (*Case* 3).—Tegmentum of mid-brain (Prussian blue reaction for iron, section otherwise unstained). Only structures which contain iron can be seen distinctly. Some of the globules show iron in concentric rings. The shadowy appearance of some of the globules is due to their containing little or no iron. The dense network of neuroglia in which the globules lie is of course here unstained. Originally × 500, but reduced to two-thirds.

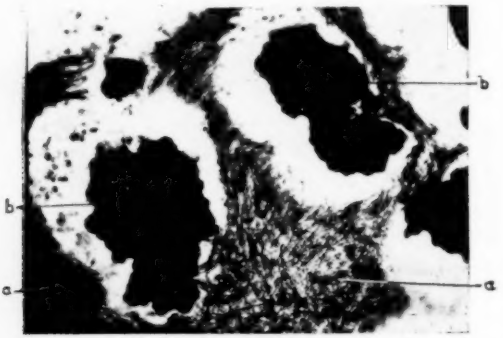


FIG. 10 (*Case* 3).—Tegmentum of mid-brain (Anderson's mordant and methyl violet). *a*, Overgrowth of neuroglial fibres and cells. *b*, Gritty deposit. Originally × 280, but reduced in illustration to two-thirds former size.

iron. The large concretions gave practically none except at the extreme edge. The fine granules along one or two capillaries gave an iron reaction. No reaction occurred with silver nitrate, but the sections had unfortunately been in formalin some time before they were examined.

The iron-containing deposit in the vessel walls in the dentate nucleus gave a phosphate reaction.

Sections of cerebral cortex, corpus striatum, dentate nucleus of the cerebellum, mid-brain, pons and medulla were stained for neuroglia. The first three regions showed some slight degree of neuroglial overgrowth, the last three great overgrowth. The maximum changes were observed in the mid-brain, and particularly in the region where the gritty deposit occurred. The extreme density of the neuroglia round the deposit is shown in fig. 10. A short distance away from the deposit

FIG. 11 (*Case* 3).—Mid-brain. (*a*) Dense overgrowth of neuroglia in vicinity of deposit. (Methyl violet preceded by Anderson's mordant.) × 500.

numerous large spider cells were visible, many of them being observed to be binucleated. Giant spider cells were occasionally seen. Close to the nerve-cells of the red nucleus were seen spider-like neuroglia cells, and in one or two instances their processes seemed to pass from one side of the cell to a vessel and from the other to a nerve-cell. It was difficult to avoid the conclusion that the gritty material may have had a share in producing the dense neuroglial overgrowth. In the pons and medulla the neuroglia was most in evidence in the region of the fourth ventricle.

The small area of mid-brain containing the deposit was unfortunately all used for histological purposes. An attempt was made to extract

adjacent cerebral tissue (which, however, contained no obvious deposit) with acetic acid, but the resulting liquid would not filter, and was too opalescent to use in testing for calcium. An ashing of the cerebral tissue was, therefore, the only way of deciding if increased calcium was present, but none of the area containing the deposit was available for analysis.

The pituitary weighed 0·7 grm. This is greater than the normal weight. Histological examination showed that it was very abnormal. Due allowance being made for post-mortem changes which readily occur in this organ, there were evidences of necrosis in the pars anterior. A very large amount of colloid was present in the pars intermedia, and the latter had proliferated and invaded to an extraordinary extent the pars nervosa. (A full account of this pituitary will be given elsewhere.)

Discussion on Case 3.

Calcification in epidemic encephalitis has now been described by many people. The deposit has not always been examined for the presence of iron. Dürck [9] stated that it was absent in his cases. Spatz [20] found it in two instances.

As regards actual increase in calcium, there seems to be no record that any quantitative chemical estimations have been carried out by anyone, and, as will be seen later, no other method is conclusive—particularly in proving the absence of calcium.

The presence of advanced morbid changes in the pituitary in Case 3 is of interest—as although several cases showing clinically signs attributed to pituitary involvement have been recorded, definite changes in the pituitary have not actually been observed histologically [13].

Carbon Monoxide Poisoning.

It was thought that it would be of some interest to examine the brain in coal gas poisoning, as rapid calcification has been described by several people in this condition. A rabbit was accordingly subjected to coal gas, and killed twelve days later. There were numerous deposits containing iron in the medulla, pons and cerebral cortex. These appeared to consist entirely of small hæmorrhages and thrombosed vessels.

General Paralysis.

The presence of iron in the pigment of the adventitial spaces of the vessels in general paralysis was first noted by Bonfiglio [2], but little is known of its exact nature.

Six brains from cases of general paralysis were examined, the cerebral cortex being the chief region investigated. In two cases the corpus striatum and dentate nucleus of the cerebellum were also examined.

Iron—showing by the Prussian blue reaction—was found in five out of the six cases, which are very briefly summarized below.

Case	Age	Duration of disease	Wassermann reaction	Iron reaction	Other remarks
(4) J. B.	48	..	Strongly positive	Markedly positive	Great neuroglial overgrowth
(5) G. T. W.	49	Some years	Positive	Negative	Some neuroglial overgrowth but not marked
(6) A. B. H.	47	Some years	Positive	Positive	
(7) R. G. S.	44	Not known	Positive	Positive	
(8) T. S.	62	Five years	Positive	Positive	
(9) A. S.	46	More than five years	Positive	Positive	

With the exception of Case 7 (R. G. S.) all the above had been treated with malaria for varying periods of time.

The iron was present in the form of small granules in the yellow pigment situated chiefly in the outer coat of the vessels. The iron seemed to be confined to the pigment masses. Not all of the pigment, however, gave an iron reaction, but it all showed a marked reaction for fat with Scharlach R. No reaction indicating phosphates was given with silver nitrate.

A pure hæmatoxylin solution caused the granules to darken somewhat.

The properties of the iron-containing pigment in the brain in general paralysis were compared with those of the iron-containing pigment, hæmosiderin, present in the liver in pernicious anæmia.

The pigment in the liver in a very advanced case of pernicious anæmia gave a marked reaction for fat with Scharlach R., darkened somewhat with a pure hæmatoxylin solution, and gave no reaction for phosphates with silver nitrate. The Prussian blue reaction was intense, but by no means all the pigment was iron containing. The solubilities of hæmosiderin in acetone, alcohol, ether, chloroform and boiling concentrated acetic acid was tested, but it seemed completely insoluble in all these solvents. It was, however, soluble in nitric acid. Prolonged immersion in hydrogen peroxide seemed to cause some bleaching of the pigment, but the iron reaction was unaltered.

Sections from the cerebral cortex in Case 4, in which the amount of iron-containing pigments was very large, were treated with the same reagents as the pernicious anæmia liver. The cerebral pigment showed the same degree of insolubility.

Hæmosiderin is stated by most authorities to be a mixture of substances rather than a definite chemical entity. It is impossible to say definitely that the iron-containing pigment in general paralysis is exactly the same substance as the hæmosiderin in the liver in pernicious anæmia, but the properties of the two pigments seem identical.

This iron-containing pigment was not quite so great in the corpus striatum and dentate nucleus as in the cerebral cortex in the two cases in which these were examined.

General Discussion.

Angiomata of the brain are not very common. Cushing [5] in an examination of over 1,100 cerebral tumours gives the figure as 0·9 per cent.

Hellmuth Deist [7], who described one case of angioma racemosum, states that he has found about twenty cases in the literature, one with calcification. The cases usually die from status epilepticus.

Calcification is not recorded in angiomata in other organs. It is apparently more common in angiomata of the brain than Deist's statement would lead one to suppose. (See reference [8], [21], [16] and [1].)

The process may occur owing to the nervous tissue in the region of the angioma undergoing degeneration and the phosphoric acid set free tending to attract calcium. The presence of hard concretions, some containing little or no iron, in the pons, and some very thickened vessels with no iron in their walls in the calcified patch in the frontal lobe in Case 2, makes it incredible that in this particular case the deposition of iron is the primary event. Calcified material is often stated to possess an attraction for iron. It appears improbable that the source of the latter can be only the degenerated nervous tissue, as the amount of iron found in Cases 1 and 2 seems too large to be thus accounted for. However, the amount of iron found by chemical analysis is the sum of that in the hæmoglobin of the blood (which is here much greater in amount than normal) and that in the deposits, and it is impossible to gain an idea of their relative importance. Decomposition of hæmoglobin would afford an obvious fluid supply of iron, but consideration of numerous sections makes the writer decide against an easy explanation of the process as calcification occurring in a hæmorrhage. This will probably be also obvious from some of the photographs, e.g., the deposit of granules along the capillaries in fig. 5. The absence of pigment in the concretions is noteworthy.

On the other hand, a microscopic hæmorrhage could be a source of iron to neighbouring tissues, extravasated blood being first broken down into hæmosiderin, and then into simpler and soluble iron compounds which could be absorbed by calcified or non-calcified deposits. However, microscopic hæmorrhages were not a feature, not being observed in Case 1, and only suspected in one area in Case 2. Another possibility is that the blood in an angioma has an abnormal composition, a dark brown pigment (non-iron containing) being observed in the blood, indicating perhaps some breaking down of hæmoglobin.

In the epidemic encephalitis case a similar pigment was observed in the blood in the vessels. However, in this disease microscopic hæmorrhages are well known to occur (Buzzard and Greenfield [4]) and were observed in this instance, though not in the area of the gritty deposit. Some of the globules showed iron deposited in concentric rings (fig. 9), resembling very much the phenomenon first described by R. E. Liesegang. The latter found that if a silver nitrate solution were added to gelatin containing chromate the resulting silver chromate was deposited in a series of concentric rings.

A similar experiment succeeds, although slowly, if to a weak gelatine solution containing phosphate in a test tube a solution of either ferric chloride or calcium chloride is added. After a few days two or three concentric rings of ferric phosphate or calcium phosphate with comparatively clear intervals between are visible. If a very stiff gelatine is used no concentric rings are obtained, but only a mass of insoluble phosphate at the junction.

In view of the fact that normal cerebral tissue contains almost twice as much magnesium as calcium, the absence of anything but a faint trace of magnesium in the deposits is rather striking.

In reviewing the literature (reference to much of which is given in recent papers by Hurst [15] and Da Fano and Perdrau [6]), it is noteworthy that many people who have recorded calcification have omitted to test for iron. On the other hand it is sometimes mentioned as being absent. The presence of calcium has not often been actually proved, many of the tests used neither demonstrating conclusively its presence nor its absence. This is due to there being no microchemical test that is infallible in demonstrating calcium, even when the latter is present in very large amounts. This fact is not usually recognized by histologists.

An association between the deposition of calcium and iron has sometimes been noted. For instance, according to Gierke [11], in the

fœtus the entire skeleton contains iron as far as it has been calcified, and most at the points of active ossification.

E. W. Hurst [15], in an interesting recent paper on "calcification" in the basal ganglia in many different conditions, finds that iron is present in a considerable number. He also remarks on the fact that the colour reactions of hæmatoxylin with iron are similar to those given by calcium. This fact was noted also independently in the present investigation. However, there is no conclusive proof that calcium is absent in all these cases. It seems to be inferred from the tests used that calcium is absent, viz.: (1) as it was impossible to produce gypsum crystals with sulphuric acid, and (2) to obtain a characteristic colour reaction with hæmatoxylin after removal of the iron with oxalic acid.

It is somewhat remarkable that the first test, which has been used by many workers on the subject, has come to be generally accepted as a sensitive one for calcium in the tissues. The solubility of calcium sulphate in water (1 part in 560) is greater than is generally recognized.

In sulphuric acid calcium sulphate is still more soluble. It is a possible, but not a sensitive, reaction to obtain gypsum crystals by treating with sulphuric acid a section containing a calcified deposit. In sections of cerebral cortex from Case 1, on treatment with sulphuric acid, crystals of calcium sulphate were not demonstrated with certainty, although chemical analysis showed that more than 500 times the normal amount of calcium was present. In sections from Case 2 (in which the deposit contained about 3,000 times the amount of calcium in the same weight of normal cerebral tissue), gypsum crystals were obtained readily after the sections had been a few minutes in sulphuric acid (fig. 8). While therefore the test is an excellent one for calcium where it succeeds, the failure of the reaction does not show the absence of calcium.

The second test could fail to occur with abundant calcium present as an acid salt. It was found in test tube experiments described at the beginning of this paper, that the colour given by any calcium salt with hæmatoxylin is entirely dependent on the reaction of the solution, the addition of a small quantity of even a weak acid, such as phosphoric, causing the so-called characteristic colour to disappear. Oxalic acid has the same effect. After treatment of sections with oxalic acid, it is difficult to remove all the acid unless alkali is used, and the presence of a slight excess of acid would in any case prevent a colour reaction with hæmatoxylin.

The question as to whether calcium or iron are usually deposited

together or as to whether one is the pioneer, will not be settled conclusively without quantitative analysis of the brain in different conditions. It has been shown in the present investigation that some calcified masses and granules in a deposit may contain no iron. It would be interesting to know whether there is any deposition of calcium in the brain in diseases where calcium metabolism is definitely disordered. Such investigations are being carried out at present. With regard to the deposition of iron, Spatz [20] mentions two cases of pernicious anæmia in which the brain was investigated and the iron found not to be increased, although the amount in the liver and spleen was very large.

Summary.

(1) A staining reaction with hæmatoxylin is not a suitable method for testing for calcium in the central nervous system. Not only may other salts give a similar reaction but also a purely organic deposit may stain. Conversely the reaction may fail in the presence of abundant calcium if the latter occurs as an acid salt.

(2) No microchemical reaction—including the formation of calcium sulphate crystals by treatment with sulphuric acid—is sufficiently sensitive to serve as a commonly applicable test for increased calcium in the brain.

(3) Two cases of calcification in angiomata of the brain are described. Microchemical reactions show that iron is present in some regions, and absent in other areas. Chemical analysis shows that the deposit contains calcium and iron, phosphates, carbonates and traces of magnesium. The calcium occurs as phosphate and carbonate, the iron partly as phosphate, partly as some other insoluble compound which is not hæmosiderin.

(4) In one case of epidemic encephalitis iron was present in the walls of the blood-vessels of the dentate nucleus of the cerebellum. A small amount of iron-containing deposit was present in the corpus striatum, but this was not marked. The tegmentum of the mid-brain contained a deposit of concentric masses similar in structure to the so-called "psammoma" bodies. Some of these structures gave an iron reaction, but other similar bodies contained little or no iron.

(5) In one case with an extreme degree of calcification in the corpora striata, and dentate nuclei of the cerebellum, but none in the mid-brain, no signs of Parkinsonism were observed clinically. The epidemic encephalitis case, in which the condition of Parkinsonism was extreme, showed only slight deposits in the corpora striata and

dentate nuclei, but a fairly large deposit in the mid-brain—and changes both in the nerve cells of the red nucleus and substantia nigra.

(6) In five of the six cases of general paralysis of the insane, iron-containing pigment was found in the walls of the blood-vessels, particularly of the cerebral cortex. Histologically this deposit does not resemble that in the two cases of angiomata of the brain nor that in epidemic encephalitis. In staining reactions and solubility it closely resembles the hæmosiderin in the liver in a case of pernicious anæmia.

The writer wishes to thank the Medical Superintendent and senior medical officers for providing facilities for studying the cases on which this investigation is based: Dr. F. Back, the pathologist, for the supply of pathological material; and Mr. C. E. Stewart for assistance with photomicrography.

She is indebted to Professor Leathes for some helpful suggestions on the chemical side.

The expenses of the research were defrayed by a grant from the Medical Research Council.

REFERENCES.

[1] Beadles, C. F. *Arch. of Neurol.*, 1899, vol. **1**.
[2] Bonfiglio, F. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, Ref. Bd. 1911, **3**, 718.
[3] Bramwell, B. *Edinburgh Med. Journ.*, July, 1886
[4] Buzzard, E. F., and Greenfield, J. G. *Brain*, 1919, **42**, 337.
[5] Cushing, H. *Lancet*, 1925, **209**, 960.
[6] Da Fano, C., and Perdrau, J. *Journ. of Path. and Bact.*, 1926, **29**, 195.
[7] Deist, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1922, **79**.
[8] Dürck, H. *Atti del I. Congresso Internaz. di Patol., Torino*, 1911.
[9] *Idem. Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1921, **72**, 175.
[10] Gans, A. *Brain*, 1923, **46**, 123.
[11] Gierke, E. *Virchow's Archiv*, 1902, **167**, 318.
[12] Guizzetti, P. *Riv. di Patologia nervosa e mentali*, 1915, **20**, 193.
[13] Hall, A. J. Monograph on "Epidemic Encephalitis," 1924, p. 52.
[14] Head, G. D. *Arch. of Int. Med.*, 1917, **20**, 24.
[15] Hurst, E. W. *Journ. of Path. and Bact.*, 1926, **29**, 65.
[16] Oberndorfer. *Verhandl. der Deutsch. path. Ges.*, 1912, **15**, 316.
[17] Obersteiner, H. *Brain*, 1884, **7**, 289.
[18] Oppenheim, H. "Text-book of Nervous Diseases," translated by A. Bruce, 1911 **ii**, p. 847.
[19] Spatz, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1922, **77**, 261.
[20] *Idem. Ibid.*, 1921, H. 1/2, 25.
[21] Vanzetti. *Archiv. di Biologia norm. e Patol.*, 1894, **58**.

OPTIC NYSTAGMUS AND ITS VALUE IN THE LOCALIZATION OF CEREBRAL LESIONS.

BY JAMES CHARLES FOX
AND
GORDON HOLMES.
(From the National Hospital, Queen Square, London).

IT is a familiar fact that passengers on a fast travelling railway train develop a more or less regular nystagmus when they watch the countryside through which the train passes. This nystagmus consists of two phases, a rapid jerk of the eyes in the direction in which the train moves, and a slower excursion in the opposite direction. In other words there is a slow deviation of the eyes in the direction of relative movement of the scenery and a rapid jerk in the opposite direction. Bárány originally introduced this as a clinical test, or rather a modification of it in which the viewed objects moved while the patient was stationary. He employed a rotating drum on which figures or vertical lines were marked. When such a drum is rotated from the patient's right towards his left side, that is in a clockwise direction when viewed from above, a nystagmus develops which consists of slow deviations of the eyes towards the left and rapid jerks which bring the eyes back to the central position or just beyond it. Consequently, we obtain a nystagmus to the right, for nystagmus is customarily designated by the direction of its rapid phase.

This nystagmus has been termed "railway nystagmus," "optomotor nystagmus" or simply "optic nystagmus." We will employ the last term in this paper, selecting it chiefly on the grounds of convenience, although it may not be the most suitable. This reaction has been already investigated in numerous cases, both in normal persons and in patients subject to various pathological conditions, chiefly by otologists, such as Bárány and Brunner, and by ophthalmologists such as Ohm, but it has also been applied to clinical neurology by Stenvers, Cords and Strauss. A good deal of discussion has arisen as to its exact nature and origin. Bárány originally believed it was a subcortical reflex, but later he came to regard it as a phenomenon of cerebral origin. In this

all subsequent observers agree with him. Bárány has also suggested that the slow phase is activated from the gyrus angularis and the quick phase from the frontal lobe. Stenvers believes that it is a cerebral reflex subserved by a path between the occipital pole or the calcarine region and the frontal lobe, and that it is lost towards the opposite side when a lesion damages either of these centres or the pathway between them. Strauss on the other hand assumes that the nystagmus is abolished only by a blindness to the one side, that is a homonymous hemianopia, or a defect of visual attention to that side.

Our chief aim in this investigation has been to determine if an absence or modification of optic nystagmus to the one side has any value in the localization of cerebral lesions. We do not intend to take part in the controversies which have already arisen regarding its nature, some of which are based on scanty evidence, though the numerous clinical and pathological observations we are able to publish will, we hope, prove of value in further investigations.

Our observations have been made on forty-one cases of cerebral tumour, in twenty-four of which the site of the lesion was verified by either operation or post-mortem examination; five cases of traumatic injury of the brain; eighteen patients with vascular lesions, in only one of whom were we able to determine the position of the lesion by autopsy; and two cases of cerebral syphilis. We have also examined a certain number of patients with visual defects due to subgeniculate lesions, including nine cases of chiasmal injury the result of pituitary or supra-pituitary tumours, cases of tabetic optic atrophy and patients with central scotomata. Further, we have included two local lesions of the cerebellum due to removal of tumours, in which nystagmus occurred on lateral deviation of the eyes; two cases of eighth nerve tumours; and three cases of tumour of the brain-stem. In addition a large number of normal persons, or patients without evidence of gross cerebral disease, were examined.

One advantage of the method in its clinical application is that it can easily be employed in practically all patients, provided any vision remains. We have obtained perfectly normal optic nystagmus with vision limited to a small portion of the field of one eye, and in cases in which central vision was so much reduced that the patient was able to count fingers only within the distance of half a metre from his eyes. Further, no high degree of intelligence or active co-operation on the part of the patient is necessary; it can often be obtained in drowsy patients if they are sufficiently sensible to direct their eyes to the drum. Optic

nystagmus can be easily elicited in children, in fact Bárány has obtained it even in an eight-hour-old infant.

We have employed a drum 16·5 cm. in diameter, which was rotated at a uniform rate by means of a string running on a pulley wheel on its axis. A series of pictures was fixed on the drum at regular intervals apart. Previous observers have used chiefly a drum with vertical black lines on a white surface, but we obtained such good results with coloured figures that we have adhered to this method. The optimal speed of rotation was found to be about ten revolutions in fifteen seconds, that is to say, the surface of the drum moved at approximately 34 cm. per second. The drum was placed about 60 cm. from the patient's face. When possible the patient was in the upright sitting posture, but sometimes it was necessary, owing to the state of the patient, to make observations as he lay prone in bed; then the drum was held in such a position that the eyes were directed to it when they were in their primary central position. In the majority of our cases observations were made with the drum rotating in a vertical axis only as the patient sat in front of it, but in a certain number vertical nystagmus was produced by rotating the drum on a horizontal axis.

The nystagmus, as we have already mentioned, consists of two phases—a slow movement of the eyes in the direction of the rotation of the drum and a rapid phase which carries the eyes back to their primary central position, or more usually a short distance beyond it. In describing it four points must be observed: first the rate of the oscillations; secondly their range; in the third place the regularity of both range and rate; and finally whether the nystagmus persists during the entire period of rotation of the drum, or tends to tire and die out. The rate and range naturally vary with the rate of rotation of the drum; the more rapid its revolutions are, the finer and more rapid is the nystagmus. There are also considerable individual variations; in some persons the oscillations are small in range and rapid in rate, in others they are wider and slower. An essential feature is that the response is similar and equal to the right or to the left as the drum is rotated in the clockwise or anti-clockwise direction, no matter what the character of the response may be. In normal persons the nystagmus is, to the naked eye at least, regular in both rate and range, and persists as long as the drum continues to rotate at a uniform rate. This feature is generally described in our notes by the statement that the nystagmus is "well sustained." In the pathological cases which we have studied, on the other hand, there may be either a complete lack of response on rotation

of the drum in one direction, or only a few isolated jerks may be obtained, or finally the nystagmus may be more irregular in rate and range, or it may tire out more quickly in one direction than in the other. This incomplete response is not uncommon in cerebral lesions, but we have chosen for publication chiefly those cases in which the response was lost to one side but normal to the other.

Unfortunately we have not tested vertical nystagmus, by rotation of the drum on a horizonal axis, in all our patients, but several observations are recorded in our notes.

The reactions of a large number of normal persons were examined to the rotation of the drum in a vertical axis. Nystagmus was invariably obtained, and in the great majority of the patients the response was equal to the right and left. A few patients, however, who presented no evidence of cerebral disease, exhibited a slight difference, either the rate and range being greater to the one side than to the other, or more commonly the nystagmus to the one side tiring out more quickly than to the other. The difference was always slight, but that it may exist must be borne in mind in interpreting the results obtained in pathological cases.

Vertical nystagmus can also be constantly obtained in normal persons, but it requires more attention and co-operation from the patient. The oscillations are not usually so regular or wide as in horizontal nystagmus. In many persons downward rapid jerks are not so easily obtained as upward nystagmus.

PATHOLOGICAL CASES.

(1) Influence of Defects of Vision.

(*a*) *Infrageniculate Lesions.*

It is remarkable with what little vision it is possible to elicit a normal nystagmus. In one woman, for instance, with advanced optic atrophy, who could count fingers only at 2 ft. with the right eye, and at 6 in. with the left, we obtained a vigorous normal response. In others good responses were obtained though visual acuity was so low that, although they could recognize the presence of figures on the drum, they were unable to distinguish their form or colour. Further, we found that defects in the field of vision had little or no influence on the nystagmus. We examined nine cases with chiasmal lesions, in which the existence of either pituitary or suprasellar tumours was confirmed

by operation or autopsy, and in all normal nystagmus to both the right and left was obtained. In some of these there were bilateral defects in the fields of vision, either in the form of bitemporal hemianopia, peripheral contraction or paracentral scotomata. In others the one eye was completely blind and there were marked defects in the temporal field of the other. We record here two observations, as this is an important matter in discussing the nature and origin of the nystagmus.

Case 1.—J. B., aged 28, a case of acromegaly, was admitted under Dr. Holmes, on March 22, 1926, and died after operation on April 17, 1926. His ocular movements were normal. His left eye was totally blind and he could only read $\frac{3}{60}$ with his right. In the right eye there was an almost complete temporal hemianopia, the blindness, even when tested with large objects, coming exactly up to the fixation point; there was obviously a defect of central

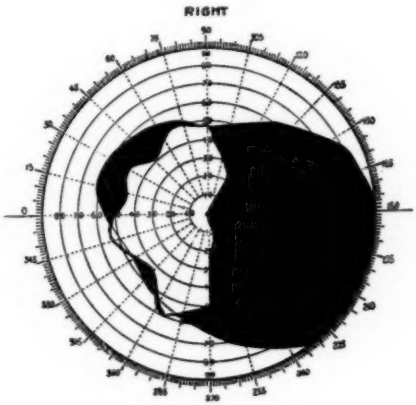


FIG. 1.

vision too (fig. 1). Normal optic nystagmus was, however, easily obtained by rotating the drum to the right or left.

Case 2.—E. P., aged 42, was admitted under Dr. Holmes on June 29, 1926. During the past six months vision had rapidly deteriorated, first in the left, later in the right eye. A radiogram revealed an enlarged and eroded sella turcica, and on operation a large soft pituitary adenoma was found compressing the chiasma and optic nerves. His visual acuity was $\frac{6}{60}$ in the left eye and $\frac{6}{18}$ in the right eye. In the left eye there was only a small area of vision in the lower nasal field, the fixation point being involved in the blindness. In the right eye there was complete temporal hemianopia extending up to the fixation point, and below it projecting for about ten degrees into the nasal field, as well as considerable contraction of the whole nasal field (fig. 2). The

nystagmus obtained by rotation of the drum in either the clockwise or anti-clockwise direction was equal and normal. It was observed, however, that on clockwise rotation the quick movement carried the eyes considerably to the right of the mid-line.

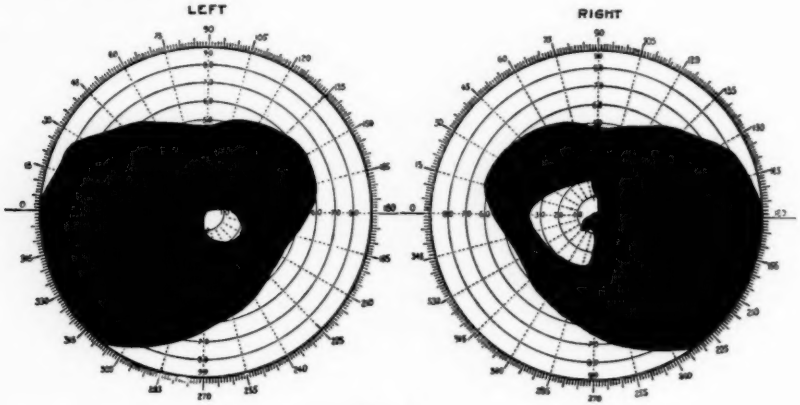


FIG. 2.

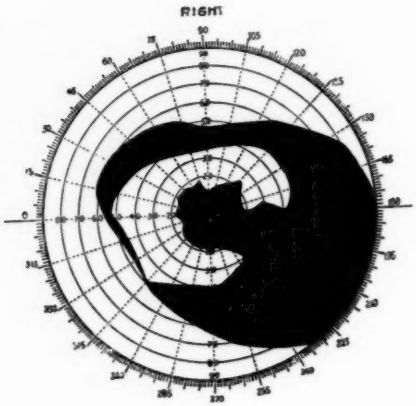


FIG. 3.

We have also found that quite normal nystagmus can be obtained in the presence of central scotomata so intense as to preclude central vision entirely. One of these cases is particularly interesting.

Case 3.—H. W., aged 42, was admitted under the care of Dr. Holmes on June 28, 1926. Vision in the left eye had begun to fail eighteen months

previously, and about this time an intense papillœdema was discovered in it. About a year before his admission his right vision was noticed to be defective. He had been operated upon by Mr. Trotter, who found a tumour in the region of the chiasma, but its removal was impossible. On examination the left eye was blind, and in the right there was a central scotoma extending out to 15° at least, with the result that central vision, even for large objects, was completely abolished; the temporal field was also much contracted (fig. 3). There was advanced optic atrophy in both eyes.

Optic nystagmus was regular, rather slow in rate, wide in range, and well sustained to both the right and left. During the test he employed extra-central vision, using only the nasal field of the right eye.

In a case of hereditary optic atrophy of the Leber type with central scotomata, in which visual acuity was reduced to $\frac{3}{60}$ in each eye, we elicited normal lateral nystagmus easily by rotation of the drum on a vertical axis.

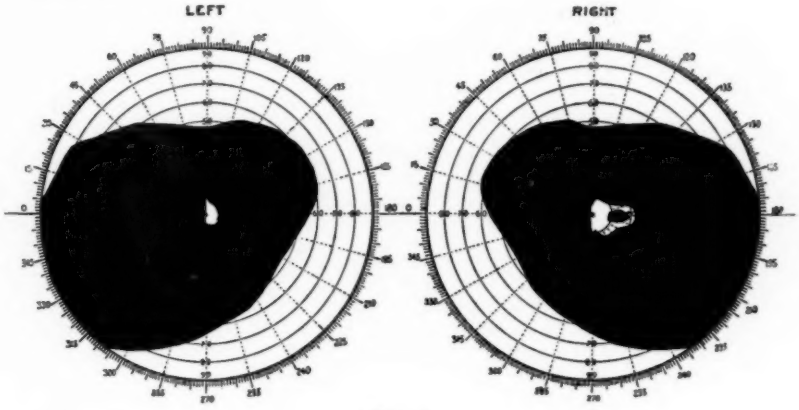


Fig. 4.

We have also obtained normal optic nystagmus in two cases of homonymous hemianopia due to injury of the one optic tract. One of them is worthy of record:—

Case 4.—M. T., aged 40, found that vision in the left eye was defective in March 1925. Since that date vision in both eyes has gradually deteriorated. She has become aware that she has practically only central vision. For three months she has been unable to recognize colours. For fifteen months she suffered with headache which has been sometimes severe, and a few attacks of unconsciousness. At present the right abdominal reflex is diminished and there is an extensor plantar response on the right side. The ocular movements are normal. The pupils are equal and react to light thrown in from her right,

but fail to contract when light falls only on the blind halves of her retinæ. Vision in the right eye is $\frac{6}{36}$, in the left less than $\frac{6}{60}$. Both optic discs are pale. Investigation of the visual fields shows in each eye a small area of vision to the right of the fixation point, somewhat larger in the right than the left. In each eye the blindness extends right up to the fixation point. The blind spot in the right eye is also much enlarged (fig. 4).

Optic nystagmus—A regular well sustained nystagmus of moderate range and rate was obtained to rotation to both the right and left.

(*b*) *Supra-geniculate Hemianopia.*

We have unfortunately not been able to examine any anatomically verified cases of hemianopia due to cortical lesions, but our observations can leave no doubt that normal optic nystagmus can be elicited despite the presence of homonymous hemianopia due to lesions of the optic radiations. During our investigation we have been able to examine many patients with such hemianopia; in some of these, it is true, optic nystagmus to the hemianopic side was either lost or disturbed, but as in numerous cases the nystagmus was normal, the hemianopia cannot be regarded as the causal factor. We may record one such case here.

Case 5.—S. P., aged 36, was admitted under the care of Dr. Holmes on June 25, 1926. In March, 1918, he was wounded by a fragment of shell-casing which entered his skull 2 cm. below and to the left of the inion. At this time he came under the care of one of us (G. H.) in France. An X-ray plate revealed a large piece of metal in the temporal lobe, about 1 cm. behind the base of the posterior clinoid process and 4·5 cm. deep from the left side of the skull. In its course the missile damaged the left side of the cerebellum, passed horizontally through the left occipital lobe and through the internal capsule. He had at first a complete right-sided hemiplegia without disturbance of speech. He was not able to walk for two and a half years, and has regained very little movement in his right arm. There was at first a complete right homonymous hemianopia, and marked cerebellar signs in the left limbs.

Examination.—There was a severe degree of right spastic hemiplegia; he could walk, but had no useful movement of his right arm. The right side of his face was also weak and his tongue deviated to the right. The left-sided cerebellar signs had almost entirely disappeared. His mental state was normal, but he was subject to attacks of severe headache.

Vision.—Acuity was $\frac{6}{6}$ in each eye. His fundi were normal. There was still a right-sided hemianopia reaching the fixation-point on the right side, and to within 2° of it in the left (fig. 5).

Optic nystagmus.—Clockwise rotation of the drum elicited a regular nystagmus to the right, of wide range and moderate rate, which was well sustained. Anti-clockwise rotation evoked a similar nystagmus to the left.

From these observations we can certainly conclude that visual defects alone, either in the form of homonymous hemianopia due to either supra- or infra-geniculate lesions, bitemporal hemianopia, or central scotomata, do not alone abolish or disturb optic nystagmus. Furthermore, optic nystagmus can be obtained even when vision is so much reduced that the patient is not able to recognize the figures on the drum or distinguish their shape or colour, provided he can perceive their presence.

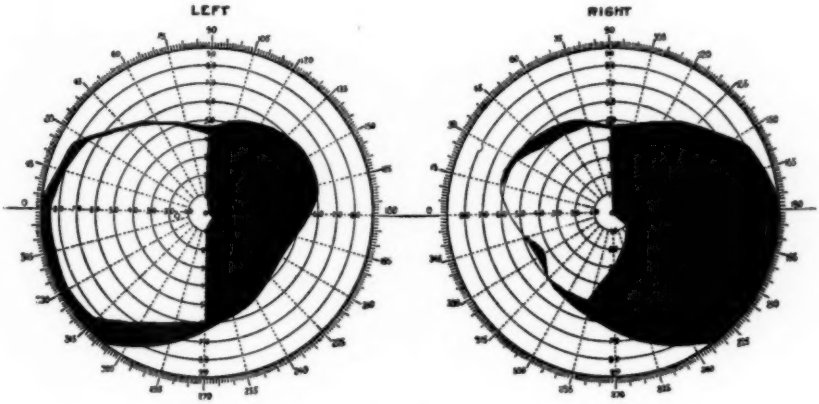


FIG. 5.

(2) VERIFIED CEREBRAL LESIONS THAT DISTURBED OPTIC NYSTAGMUS.

(*a*) *Verified by Autopsy.*

We have selected for publication seven cases with loss of optic nystagmus in which the lesion was verified by autopsy. In each of these we give a short résumé of the chief clinical features of the case, record the state of vision and of the visual fields, and describe the reaction of the eyes to rotation of the drum on a vertical axis. In some cases the movements of the eyes observed when the drum was rotated horizontally are also recorded. Finally, we describe the site of the lesion as revealed by post-mortem examination. In many of these cases repeated examinations of the eyes were made, but the separate observations have been recorded only when the results varied materially. We have, however, always described the last observations which were made preceding death.

Case 6.—N. W., aged 44. Admitted under the care of Dr. Riddoch on January 5, 1926. Died February 16, 1926.

On December 14, 1925, she suddenly lost power in her right arm and leg and was unconscious for a brief period. Speech was only slightly affected. Recently she had noticed numbness of her right side. There has been very little recovery of function.

Examination.—The patient was in a dull inattentive state, and had a mild degree of aphasia. Her blood-pressure was very high.

There was a complete right-sided spastic hemiplegia, the right side of the tongue and face being involved. All forms of sensation were impaired on the right side, and there was complete astereognosis in the right hand. The deep

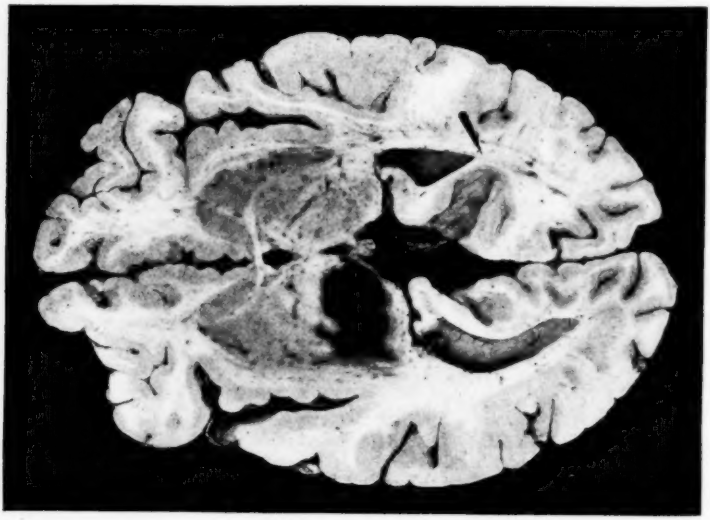


FIG. 6.

reflexes of the right side were exaggerated and the right plantar response was extensor. The ocular movements were full and normal. The right pupil was larger than the left, and both reacted sluggishly to light and accommodation.

Vision.—Acuity was $\frac{6}{18}$ in the right eye, $\frac{6}{6}$ in the left. The ocular fundi were normal, but the discs were slightly blurred. The visual fields were normal to rough tests, but careful perimetric examination was impossible.

Optic nystagmus.—Clockwise rotation of the drum elicited only an occasional coarse jerk to the right; sometimes no movement of the eyes occurred. Anti-clockwise rotation produced a regular nystagmus to the left of large amplitude and well sustained.

On the night of February 4 the patient woke in a very agitated state, speech

was unintelligible, the eyes were deviated to the right, there was a left-sided ptosis, and weakness of the left external rectus and of the left side of the face. She died twelve days later.

Autopsy.—The cerebral arteries were thickened and irregular in calibre. A series of horizontal sections were made through the brain after hardening. In a section through the upper level of the thalamus an organized hæmorrhage was found on the left side, extending backwards from the posterior margin of the head of the caudate nucleus to the posterior margin of the lenticular nucleus. Here it destroyed the posterior limb of the internal capsule and part of the central white matter lateral to it. At the level of the inferior surface of the corpus callosum the hæmorrhage occupied the posterior half of the thalamus and the posterior part of the posterior limb of the internal capsule. In a lower section through the anterior and posterior commissures the lesion was smaller and lay almost entirely within the thalamus, only a small projection extending into the retrolenticular segment of the internal capsule. The external geniculate body escaped, as well as the majority at least of the fibres of the optic radiation passing from it (fig. 6).

A more recent hæmorrhage had destroyed the left side of the pons at the level of the trigeminal roots; two slender projections from it extended into the mid-brain, one through the left crus, the other into the tegmentum. This hæmorrhage was evidently the cause of the terminal symptoms and of death.

In this case the pontine hæmorrhage, which occurred twelve days before death, had obviously nothing to do with the disturbance of optic nystagmus as previously observed. This must be correlated with the organized hæmorrhage which destroyed the posterior limb of the internal capsule, the white matter lateral to it, and part of the thalamus.

Case 7.—R. C., aged 44. Admitted May 3, 1926, under the care of Dr. Holmes. Died May 8, 1926.

Left frontal headaches, associated with dizziness, began six weeks before admission to hospital. Soon after vomiting occurred frequently. Diplopia, most marked on looking to the left and upwards, first developed two weeks ago. The pain in the head was still confined to the left side and was excruciating. Impairment of memory has been observed during the last few weeks.

Examination.—Patient was alert and well oriented. No mental disturbance was observable.

There was no diminution of power, incoordination, tremor or other involuntary movement of the limbs, but the right arm when outstretched fell slowly away when the patient closed his eyes. The face, tongue, jaw and palate moved symmetrically. The only disturbance of sensation was a diminution of the appreciation of vibration in the right hand and foot. The reflexes were all normal, apart from a diminution of the right abdominal. Examination with coloured glasses revealed a slight weakness of the left superior and external recti. During examination the patient developed a clonic twitching of his

right arm with loss of tone; sensory stimulation accentuated the twitching. He became confused and aphasic, the right side of his face moved poorly on voluntary effort and his tongue deviated to the right. During and for a short time after the attack the discrimination of compass points was lost in his right hand, but cutaneous sensation, the sense of position and stereognosis remained normal.

Vision.—Central acuity was $\frac{6}{9}$ in each eye. On both sides there was intense papillœdema. The only change in the fields of vision was a slight peripheral restriction of the right nasal field.

Optic nystagmus.—Clockwise rotation of the drum evoked at first a few coarse jerks of his eyes to the right, there was no further movement. Anti-clockwise rotation caused regular nystagmus of moderate rate and range, which was well sustained.

On May 7 Mr. P. Sargent opened the skull over the left temporal lobe, Intracranial pressure was very high. The temporal gyri were soft to palpation, but exploratory punctures revealed no tumour. The patient died on the following day.

Autopsy.—On removing the brain a tumour was found on the under surface of the left temporal lobe, midway between the occipital and temporal poles and just lateral to the collateral sulcus. It was soft and contained yellowish glairy fluid. On section of the brain a small tumour was seen in the white matter of the temporal lobe lateral to the posterior angle of the lenticular nucleus, extending upwards towards the optic radiations, the inferior fibres of which were probably involved as they turned around the horn of the ventricle. The tumour was a glioma.

In this case there was a small localized tumour in the basal portion of the left temporal lobe, which extended upwards to the occipital sagittal strata. This was the only lesion in the brain, and to it must be attributed the loss of optic nystagmus to the right.

Case 8.—W. B., aged 31. Admitted February 4, 1926, under the care of Dr. Collier. Died February 28, 1926.

In 1922 the patient was struck on the head in the right frontal region by the butt of a rifle. He became unconscious and remained so for four days, after which his recovery was uneventful.

In September, 1923, following a collision with another football player, he had a fit, during which the right side of the mouth was drawn up and the right arm and leg twitched for twenty-five minutes. Unconsciousness followed for forty-five minutes; the right arm and leg were weak for two weeks and speech was imperfect for five days. For one month later he had severe right-sided headaches and vomiting.

There were no further symptoms until October, 1925, when he had a series of right-sided attacks with unconsciousness during a period of thirty-five minutes. Complete motor aphasia followed recovery of consciousness. He

had not regained power of speech, but could understand spoken and written language. The right arm and leg have remained weak.

For three days previous to admission he had had complete right hemiplegia and been semi-comatose.

Examination.—The patient was inarticulate, but had no sensory aphasia. He had a complete right flaccid hemiplegia, including the face. There was no sensory loss. The deep reflexes were slightly increased on the right side. The right abdominal reflex was absent. Both plantar responses were flexor.

Vision.—Acuity was not tested. The fundi were normal. The visual fields were full to rough test and there was no visual inattention.

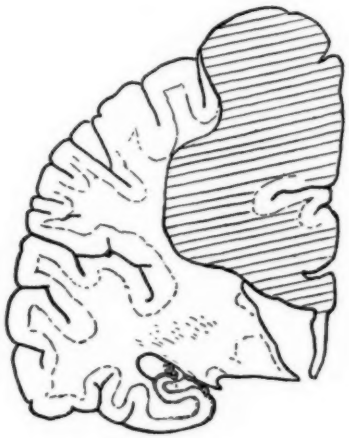


FIG. 7.

Optic nystagmus.—Clockwise rotation of the drum elicited only an occasional jerk, nothing suggesting nystagmus. Anti-clockwise rotation produced a regular slow nystagmus of medium range and well sustained.

The patient died February 28.

Autopsy.—There was a large amount of bulging of the mesial surface of the left hemisphere. The tumour came to the surface at the upper end of the fissure of Rolando, in both the precentral and postcentral gyri. When the brain was cut in coronal sections the tumour was found to reach its greatest extent beneath the fissure of Rolando, where it occupied the upper and mesial portion of the white matter and infiltrated the cortex. In this region, and also more forward, it involved the corpus callosum and at one point extended over into the white matter of the right hemisphere for a short distance (fig. 7). In its forward extent the tumour reached a point 1 cm. in front of the sulcus paracentralis. It extended backward as far as the posterior end of the calloso-marginal sulcus. The tumour lay anterior to the lateral geniculate body and the optic radiations. It was a glioma.

In this case a large tumour lay in the mesial portion of the left hemisphere, in the region of the central gyri, but it extended deeply into the white matter and down to the level of the corpus callosum, which it infiltrated. It was the only lesion in the hemisphere, and must be regarded as the cause of the abolition of nystagmus to the right.

Case 9.—J. I., aged 46. Was admitted on April 20, 1926, under the care of Dr. Riddoch. Died April 30, 1926.

In February, 1926, there was a definite change of disposition; the patient suddenly dropped all his hobbies and began to sit up late at night. In March

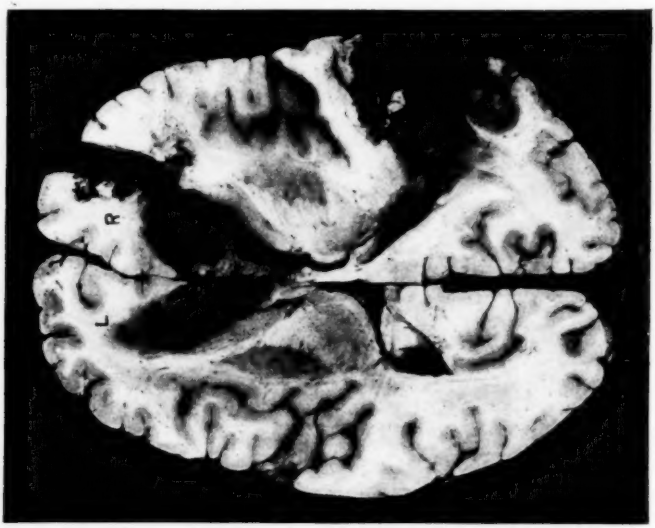


FIG. 8.

he began to complain of a smell of "peardrops," a pungent odour which left him faint, and was accompanied by a severe frontal headache. These attacks occurred three or four times a day. The headaches became worse, but the olfactory sensations have ceased.

Two weeks ago he began to vomit repeatedly and had attacks of semi-consciousness.

Examination.—He was lethargic and disoriented, and his attention was poor, but he was cheerful and facetious. No apraxia or aphasia was present.

He had a slight left-sided hemiplegia, more marked in the arm than in the leg or face, and slight increase of tone in both left limbs. There was also a slight left hemianæsthesia. All the deep reflexes were increased on the left, and the left plantar reflex was extensor.

Vision.—Acuity was $\frac{6}{18}$ in each eye. There was intense bilateral papillœdema. To rough tests there appeared to be a partial left homonymous hemianopia; perimetric examination was not possible. Four days later there was no hemianopia to moving objects, but he was unable to perceive stationary objects to the left. There was also an attention loss on the left side.

Optic nystagmus.—Clockwise rotation of the drum elicited a regular, rapid nystagmus of small amplitude, which was well sustained. Anti-clockwise rotation and rotation up and down gave no response.

On April 29, Mr. Armour operated and removed part of a tumour from the right second temporal gyrus. The patient died the following day.

Autopsy.—There was a large cavity in the posterior part of the right second and third temporal gyri from which the tumour had been removed. It had extended almost to the posterior horn of the ventricle and forwards towards the posterior segment of the internal capsule and the posterior margin of the lenticular nucleus. It had infiltrated the lower fibres of the occipital sagittal strata, but the upper segments of these were not involved. The tumour reached almost to the basal surface of the hemisphere, and upwards as high as the apex of the lenticular nucleus, and into the white matter of the supramarginal gyrus (fig. 8).

A horizontal section through the brain revealed another tumour in the genu of the corpus callosum, which extended into the white matter of each frontal lobe in an almost symmetrical manner. It compressed, but did not invade the caudate nuclei. Both tumours were gliomatous in structure.

In this case one tumour occupied the posterior part of the right temporal lobe, but it extended down almost to the basal surface of the hemisphere and upwards into the white matter of the supramarginal gyrus. A second tumour involved the genu of the corpus callosum and spread into each frontal lobe. As optic nystagmus to the right was normal and that to the left abolished, we must look on the temporal tumour as the cause of its disturbance.

On the other hand, it is possible that the absence of vertical nystagmus, which we have met with in no other case, may be related to the bilateral frontal lesion, or to the tumour of the corpus callosum.

Case 10.—F. R., aged 36. Was admitted on January 4, 1926, under the care of Dr. Gordon Holmes; she died on February 18, 1926.

During the summer of 1925 she was in hospital owing to the occurrence of right-sided epileptic attacks; as these ceased and she had then no other symptoms she was discharged. In December the attacks recurred; some began with convulsions in her right arm, others in her right leg. The right limbs gradually became weaker since December, and she had recently found some difficulty in speech.

Examination.—She was intelligent and alert. A slight degree of aphasia of the motor type was present.

There was an almost complete hemiplegia of the right side with commencing spasticity. The lower part of the right side of her face was weak and her tongue was deviated to the right. Cutaneous sensation was normal, but there was impairment of the sense of position, discrimination of compass points and of stereognosis in the right limbs. The deep reflexes of the right side were exaggerated, and the right plantar response was extensor.

Vision.—Acuity was $\frac{6}{9}$ in each eye; the fundi were normal and the visual fields were full.

On January 18 she suddenly became very ill with signs of an acute rise of intracranial pressure. Mr. P. Sargent operated and found an area of softened cortex in front of the superior genu of Rolando on the left side. On incising it a large tumour was found in the central white matter and part of it was removed.

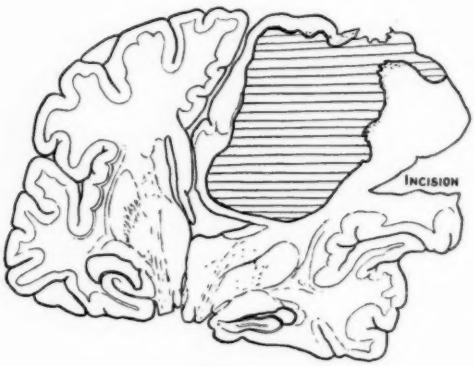


FIG. 9.

After the operation her state improved, but she still had a complete right hemiplegia and more aphasia.

Optic nystagmus.—Clockwise rotation of the drum elicited no response, no movement of the eyes occurring. Anti-clockwise rotation produced regular nystagmus to the left, slow in rate and of large amplitude, which persisted well.

In the middle of February she became aphasic and semi-comatose and died in a few days.

Autopsy.—The operative incision was found in the lower third of the post-central gyrus. The tumour did not come to the surface, but in removing the brain a thin layer of normal cortex covering it was torn through in the upper part of the left post-central convolution. Coronal sections through the brain revealed a large tumour which was partly destroyed by hæmorrhages, in the white matter of the mesial half of the hemisphere. It lay chiefly under the upper end of the fissure of Rolando and extended down to the level of the ventricle, which it compressed and displaced. In the frontal lobe it was

smaller and approached nearer to the surface. It extended backwards through the parietal lobe to the level of the splenium, still lying above the lateral ventricle, and lateralwards so far as to compress the white matter under the supramarginal gyrus. The optic radiations were not involved, and apparently not even compressed. The tumour was a glioma (fig. 9).

In this case, in which nystagmus to the right was absent, a large tumour was found in the white matter of the left hemisphere under the fissure of Rolando. It is important to note that the tumour infiltrated widely the white matter of the hemisphere of the parietal lobe. Unfortunately optic nystagmus was investigated only after the operation, in which a deep incision was made through the inferior third of the left postcentral gyrus. It is possible that it was this operative incision which abolished nystagmus to the right.

Case 11.—N. M., aged 52. Admitted November 23, 1925, under the care of Dr. Riddoch. Died December 13, 1925.

In March, 1924, a tumour was removed from her left breast. She remained well until May, 1925, when she suddenly had a Jacksonian attack starting in the two fingers of her left hand, spreading up the arm and involving the left face, without loss of consciousness. Following this the left leg and arm were paralysed for a few days. During the past six months there have been repeated attacks similar to the first, accompanied by severe occipital headache. The left arm had become very weak and she had begun to drag the left leg.

Examination.—The mental state of the patient was dull and attention rather poor.

There was a left-sided spastic hemiplegia, more marked in the upper limb; the left side of the face and the tongue were also involved; deep sensation and tactile discrimination were lost on the left side. The deep reflexes on the left side were exaggerated and the left plantar response was extensor. The ocular movements were full and normal. The right pupil was sluggish in its response to light and on accommodation.

Vision.—Acuity was $\frac{6}{60}$ in both the right and left eyes. Bilateral papill-œdema was present. Rough tests showed a restriction of the left lower quadrants of both visual fields. There was also a definite visual inattention to the left.

Optic nystagmus.—Clockwise rotation of the drum elicited a slow, regular nystagmus of medium range, which tended to tire easily. Anti-clockwise rotation caused no response. Upward rotation produced a slow irregular nystagmus which tired easily. Downward rotation caused a normal regular nystagmus which was better sustained.

December 8.—A right parietal decompression was performed and a portion of tumour removed from the right angular gyrus. The patient died December 13.

Autopsy.—There was a wound in the right angular gyrus from which part of the tumour had been removed, and beneath a large cavity extending into the

white matter of the hemisphere. A second tumour, which was firm but partly broken down and sharply delimited from the tissue surrounding it, was found in front of the cavity; it occupied the greater part of the central white matter under the fissure of Rolando. It did not extend to the level of the corpus callosum. There was a considerable amount of œdema around the tumour, which was a scirrhous carcinoma (fig. 10). Another small cancerous nodule measuring 1·5 cm. across, was found in the lateral part of the right biventral lobe of the cerebellum.

In this case the pathological lesion was much larger than had been expected; part of the carcinoma had been removed from the right

FIG. 10.—A horizontal section through the right hemisphere showing the cavity from which one tumour had been removed, and a second tumour in front of it.

angular gyrus, but a second tumour lay in front of it in the white matter of the hemisphere. It is impossible to say to which of these the abolition of nystagmus was due.

Case 12.—H. B., aged 55, was admitted March 11, 1926, under the care of Dr. Holmes. Died June 7, 1926.

The present illness began in October, 1925, with numbness and weakness of the right arm and dragging of the right foot. A month later, in November, 1925, she had a fit with clonic movements of the right arm and leg lasting ten minutes, followed by marked weakness of the right side lasting about a week. Her friends had noted right facial weakness. There have been severe frontal headaches and occasional vomiting since the onset. She had experienced some difficulty in finding the words she wanted.

Examination.—Attention and memory were poor. There was no aphasia, agnosia or apraxia.

A considerable degree of right hemiparesis was present, involving the arm

more than the leg; the right side of the face was also weak. All forms of sensation were diminished in the right side of the body, and the right deep reflexes were exaggerated; the right plantar was extensor in type. The right external rectus was weak, but the other ocular muscles were normal.

Vision.—There was a high degree of myopia; when corrected, central acuity was $\frac{3}{24}$ in each eye. Bilateral papillœdema was present. Perimetric examination revealed a general contraction of the visual fields, especially in their right halves. There was a marked loss of visual attention to the right.

Optic nystagmus.—Clockwise rotation of the drum evoked irregular slow jerks of the eyes to the right of small amplitude, the left eye moving more than the right. Anti-clockwise rotation produced regular, slow, and well-sustained nystagmus of large range.

March 19.—Mr. P. Sargent made a trephine opening over the lower portion of the left parietal lobe. There was little or no tension, but the gyri were

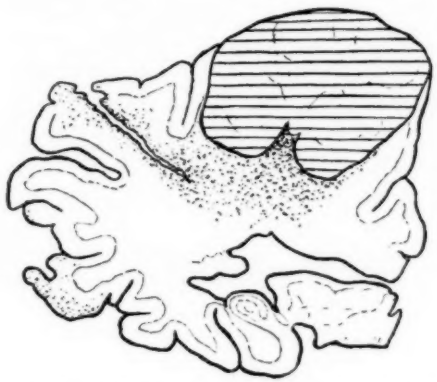


FIG. 11.—A coronal section through the left hemisphere. The position of the tumour is indicated by shading, the softening beneath it by dots. The operative incision can be seen to the left, below the level of the tumour.

flattened. No tumour was visible on the surface; an incision was made through the lower end of the postcentral sulcus, but no tumour was found.

After the operation, a complete right-sided hemiplegia developed gradually with complete right-sided homonymous hemianopia, jargon aphasia and a tendency to mirror writing with her left hand.

Optic nystagmus.—April 1: Clockwise rotation gave no response. Anti-clockwise rotation evolved fine, rapid, regular, and well-sustained nystagmus to the left.

April 10.—Clockwise rotation elicited no response; anti-clockwise rotation produced normal nystagmus to the left. Upward rotation resulted in regular nystagmus downwards and to the left at an angle of 45°; downward rotation produced a few irregular jerks upwards and to the left.

The patient was discharged from hospital on April 16, and died at her home on June 7.

Autopsy.—The rewas a large ragged hernia of the left inferior parietal, lobule and of the upper part of the temporal lobe. A large spherical tumour, 4 cm. in diameter, was found in the upper left parietal lobule, which presented on both the lateral and mesial aspects of the hemisphere. It lay behind the fissure of Rolando, but a small projection passed in front of it into the paracentral convolution. It extended down to the level of the callosomarginal sulcus (fig. 11).

The operative incision was easily identified; it extended from the lower end of the left postcentral gyrus for a depth of 3 cm. towards the ventrolateral margin of the tumour; consequently it cut across the white matter of the left inferior parietal lobule.

In this case there were two separate lesions—a tumour occupying the upper margin of the left parietal lobe, and an operative incision in the inferior end of the left postcentral gyrus and the white matter beneath it. As optic nystagmus was present, though not symmetrical, before the operation, but that to the right absent after the incision had been made, it is natural to conclude that the operative lesion in the inferior parietal lobe was the causal factor of its abolition.

(*b*) *Lesions verified by Operation only.*

We include the clinical notes of three cases in which the site of the lesion was verified by operation, and one in which nystagmus to the one side was lost after an operative incision into the opposite hemisphere. We recognize that these cases are of less value than those confirmed by post-mortem examination, since operation can rarely determine accurately the exact position occupied by the tumour, or its size.

Case 13.—L. R., aged 54, was admitted under the care of Dr. Holmes, January 7, 1926. Discharged February 20, 1926.

For the past six months the patient had noticed progressive failure of vision. She also suffered from attacks of twitching of the left side, without loss of consciousness. There has been no weakness and no disturbance of sensation.

Examination.—The patient was mildly euphoric. The head was carried slightly inclined to the left. The motor and sensory systems were entirely normal and there was no change in the reflexes. Examination of the cranial nerves revealed nothing abnormal.

Vision.—Acuity was $\frac{6}{60}$ in the right eye and $\frac{6}{36}$ in the left eye. Bilateral papillœdema was present. Perimetric examination showed the visual fields to be contracted to 30° to 40°.

Optic nystagus. January 14, 1926.—A normal and equal response was elicited on clockwise and anti-clockwise rotation.

Operation was performed January 15, 1926. Following a right fronto-temporal decompression two incisions were made into the right frontal lobe: (1) in the inferior frontal convolution in its anterior third, (2) in the middle and inferior convolutions in their posterior thirds. No tumour was found.

Optic nystagmus. January 30, 1926.—Clockwise rotation of the drum produced regular rapid nystagmus, which was well sustained. Anti-clockwise rotation elicited no movement of the eyes whatever.

Here the position of the tumour was not determined, but it alone had not in any way disturbed optic nystagmus. On the other hand, after two incisions had been made into the right frontal lobe, nystagmus to the left disappeared.

Case 14.—J. R., aged 31, was admitted under the care of Dr. Russell, April 8, 1926. Discharged May 19, 1926.

The patient began to have both major and minor epileptiform attacks in the summer of 1921. She described a typical one as follows: "There is a sick sort of feeling under the left costal arch. Then something seems to travel down the left side, followed by a noise or musical tune in the head. Often there is a bad taste in the mouth at the beginning of the attack." She then grips with the left hand and finally loses consciousness. After the attack the left arm and leg may be weak for some time, and she has often had severe headache and vomiting. Following a severe attack two weeks ago, weakness in the left arm and leg has persisted.

Examination.—Speech was slow and slightly slurred, but there was no defect of comprehension or expression. She had a partial left spastic hemiplegia, including the face. The sense of position and movement, tactile discrimination and appreciation of form were all markedly impaired on the left side. The deep reflexes were exaggerated on the left, and the left plantar response was extensor. The cranial nerves were normal.

Vision.—Acuity was $\frac{6}{9}$ in both eyes; the disc margins were slightly blurred. Perimetric examination revealed a left homonymous hemianopia, which spared macular vision on both sides.

Optic nystagmus. April 10.—Clockwise rotation of the drum produced a regular nystagmus to the right, of wide range and well sustained. Anti-clockwise rotation caused not a single jerk.

Operation was performed April 15, and a glioma the size of a ping-pong ball was removed from the anterior part of the right temporal lobe.

Optic nystagmus. April 17.—Re-examination revealed the same loss of response to anti-clockwise rotation; clockwise rotation gave a normal result.

In this case a moderately large tumour was removed from the lateral and anterior part of the right temporal lobe. Nystagmus to the left was completely absent both before and after the operation.

Case 15.—L. J., aged 46, was admitted under the care of Dr. Walshe on February 25, 1926; discharged May 7, 1926.

The patient had suffered from severe periodic headaches during the past three years. About six months ago she had a semi-conscious attack during which she had diplopia. Since this time her vision had steadily failed, and she had suffered from periods of mental confusion and occasional attacks of unconsciousness. In one of these, on December 12, there were involuntary movements, the exact nature of which was unknown.

Examination.—There was an aphasia of the sensory auditory type. Apraxia and perseveration were also present. She had a slight hemiparesis. The right plantar response was extensor. Cutaneous sensation was impaired and deep sensibility lost on the right side.

Vision.—Visual acuity was not tested. Both optic discs were blurred, but there was no swelling. There was a complete right homonymous hemianopia.

Operation was performed on March 9. A tumour was found in the left parieto-occipital region, extending deeply into the parietal and occipital lobes. No attempt was made to remove it.

Optic nystagmus. March 17, 1926.—Clockwise rotation of the drum elicited not a single jerk. Anti-clockwise rotation produced a regular nystagmus of wide range and well sustained. Upward rotation caused a regular nystagmus of wide range, downward and to the left, 60° to the vertical. Downward rotation caused an irregular nystagmus of wide range, upward and to the left, 30° to the vertical.

In this case the presence of a tumour in the left parieto-occipital region was verified by operation, but we have no idea of its size or actual position. Nystagmus to the right was lost.

It is interesting to note that in the nystagmus produced by horizontal rotation of the drum, the eyes in the quick phase always deviated towards the left.

Case 16.—R. B., aged 56, was admitted under the care of Dr. Riddoch, October 6, 1925. Discharged November 20, 1925.

The patient had suffered from tingling of the right side of the face for the past ten weeks. This came on in attacks, and later spread to include the entire right side. Weakness of the right arm was first noticed six weeks before admission. This had steadily increased and for the past month the right leg has also been involved. During the past fortnight he has experienced difficulty in finding the proper words. He has also noticed failure of vision.

Examination.—The patient had a definite paraphasia and slight degree of apraxia. There was a right spastic hemiplegia, more marked in the upper limb and including the face and tongue. The right plantar response was extensor. Sense of position, vibration, appreciation of form, topognosis and tactile discrimination were all lost on the right side.

Vision.—Acuity was $\frac{9}{12}$ in the right eye and $\frac{12}{12}$ in the left eye. Bilateral papillœdema was present. The fields were full to rough tests.

Operation was performed on October 10, 1925. The dura was found adherent to a milky gelatinous area in the left superior parietal convolution. Exploration of this area revealed a hard tumour the size of a walnut which was removed. Section showed this to be a metastatic carcinoma.

Optic nystagmus. November 7, 1925.—Clockwise rotation of the drum elicited only an occasional irregular jerk. Anti-clockwise rotation produced a slightly irregular nystagmus to the left, of small range and well sustained.

In this case, where nystagmus to the right was absent, a metastatic carcinoma was removed from the left superior parietal lobe. We cannot, however, be certain that, as so frequently occurs in malignant disease of the brain, a second lesion was not present.

In a few cases of cerebral tumour we have observed a change in the reactions of the eyes to the rotating drum with the onset of symptoms of severe cerebral compression. In some of these cases nystagmus became normal again when the pressure was relieved by the removal of the tumour; we have never observed nystagmus return to the normal after a simple decompression operation. From this we may conclude that the disturbance of nystagmus was due to local rather than to general pressure. Two of these cases are worthy of record, although they have a negative rather than a positive value as far as the localization of the mechanism of the nystagmus is concerned. In Case 17 a large lesion existed in the upper parieto-occipital region; in Case 18 a lesion was present in the lower part of the Rolandic area.

Case 17.—H. C. was admitted under the care of Dr. Holmes, October 13, 1925. Discharged November 21, 1925.

The patient began to have severe headaches in June, 1925, and soon afterwards noticed failure of vision. At times he suffered from visual disorientation, complaining that he could not find the door-knob and other objects, although he could see them. The headaches became progressively worse and were recently accompanied by vomiting. During the past two days he had become very drowsy and mentally confused.

Examination.—The patient was disoriented in time and place and his speech was incoherent. The head was inclined slightly to the left. The pulse was 50 per minute. The left arm when outstretched fell away, the left grip was weaker than the right, and the left hand was slower and more clumsy in finer movements. The sense of position and appreciation of form were completely lost in the left hand. The deep reflexes were equal, but the left plantar response was extensor.

Vision.—Acuity was not tested. Bilateral papillœdema was present. Rough tests showed a complete left homonymous hemianopia.

Optic nystagmus. October 17, 1925.—Clockwise rotation of the drum produced an irregular nystagmus of medium range and rate which tired easily. Anti-clockwise rotation elicited only a few irregular jerks.

On October 19 the skull was opened in the right parieto-occipital region. No tumour presented on the surface, but palpation revealed a soft area just anterior to the angular gyrus. An incision was made into this area and a glioma removed, which measured 4 cm. in diameter and extended deeply into the hemisphere. The cavity which the tumour had occupied lay in the upper and anterior part of the occipital lobe and the posterior and lower part of the parietal lobe, in the neighbourhood of the angular and supramarginal gyri.

Perimetric examination on November 3 showed a complete loss in the left lower quadrants of both fields and a defect coming to within 10° of the fixation point in the upper fields.

Optic nystagmus. November 7.—Clockwise rotation evoked a regular rapid nystagmus of wide range and well sustained. Anti-clockwise rotation produced a rapid regular nystagmus of smaller range and less well sustained.

The patient was discharged November 21, greatly improved. He came under observation again on March 3, 1926, when examination for optic nystagmus showed a normal and equal response to both clockwise and anti-clockwise rotation of the drum.

Case 18.—A. F., aged 46, was admitted under the care of Dr. Holmes March 26, 1926.

The patient had suffered with headaches for the past three years. During the past nine months she had been subject to right-sided Jacksonian attacks with loss of consciousness. Weakness of the right hand and slight difficulty with speech had been present for three months.

Examination.—There was a right-sided hemiparesis, including the face, and a right hemianæsthesia involving all forms of sensation, especially the sense of position and appreciation of form. The deep reflexes on the right side were exaggerated and the right plantar response was extensor.

Vision.—Acuity was $\frac{6}{9}$ in both eyes. The fundi were normal, the fields were full to rough tests.

Optic nystagmus. April 1.—Clockwise rotation of the drum produced a fairly regular and well-sustained nystagmus. Anti-clockwise rotation caused a similar response.

Optic nystagmus was re-examined on April 7, just prior to operation, at which time the patient's condition was much worse. Clockwise rotation elicited only an occasional jerk, irregular in rhythm and range. Anti-clockwise rotation produced a fairly regular nystagmus of wide range and well sustained.

On April 7 a large tumour was removed from the lower end of the left Rolandic area, chiefly postcentral, but extending forwards under the central fissure in one part.

On April 10 there was complete paralysis of the right arm, increased weakness of the right leg and slight aphasia.

Further observations for optic nystagmus were made on April 10, April 13

and May 25. On each occasion both clockwise and anti-clockwise rotation of the drum produced a normal and equal response.

(2) Local Lesions which did not disturb Optic Nystagmus.

During the course of our investigations we have met with a large number of cases of unilateral cerebral lesion in which optic nystagmus to both sides was perfectly normal. In many of these cases we could not verify the exact position of the cerebral disease, but in some we have been able to determine its site by either autopsy or operation. In Case 5, for instance, optic nystagmus was normal despite the existence of a complete homonymous hemianopia and a severe degree of hemiplegia, due to a gunshot wound through the internal capsule which was inflicted eight years prior to our examination. Cases 16 and 17 also belong to this group, as the nystagmus was absent only during the stage of intense pressure.

It is necessary to publish a few only of our observations; we have selected those which will be illustrative of points to be raised in the discussion.

Case 19.—A. F., aged 34, was admitted on April 26, 1926, under the care of Dr. Holmes.

For five years she had complained of headache, dizziness and pain in the region of the left eye. She had noticed no weakness, sensory disturbance or affection of vision.

Examination.—All motor functions were normal and there were no changes in her reflexes. Gait was natural. Investigation of sensation revealed only a defect in two-point discrimination in her right foot, and a slight diminution of the sense of position in her right toes.

Vision was $\frac{6}{9}$ in each eye. There was a moderately severe bilateral papilloedema. The visual fields were full and there was no disturbance of visual attention.

Optic nystagmus.—Clockwise rotation of the drum elicited a regular, rather rapid and well-sustained nystagmus of small range to the right. Anti-clockwise rotation produced similar nystagmus to the left.

On June 24 Mr. P. Sargent removed a large endothelioma, about 4·5 cm. in diameter, from the apex and mesial aspect of the posterior part of the left parietal lobe. The tumour grew from the arachnoid but compressed the brain severely. The patient recovered rapidly from the operation.

Optic nystagmus.—On July 2, and on subsequent examinations, the nystagmus to both the right and left was equal and normal in every respect.

Case 20.—J. R., aged 53, was admitted under the care of Dr. Collier April 28, 1924, and discharged August 6, 1924.

For two years the patient noticed a slight impairment of her mental

faculties and a failure of vision. There had been frequent severe headaches, often worse in the early morning. Recently her husband noticed that she often missed the mark in putting the cup upon the saucer or in pouring out tea, tending to deviate to the left. Also in walking she had begun to stagger to the right. She thought this might be due to her difficulty in seeing things to her left.

Examination.—The patient had transient periods of disorientation and confusion, and complained bitterly of headache. The left outstretched arm fell away, but there were no other signs of motor weakness. Pin-prick was not as well appreciated over the left side as over the right, but no other sensory changes were present. The reflexes were normal and equal. Both plantar responses were flexor. During attacks of headache and vomiting the left plantar reflex became extensor.

Vision.—Acuity was not tested. Bilateral papilloedema was present. Perimetric examination revealed a complete left homonymous hemianopia coming right up to the fixation point.

On May 27, 1924, the skull was entered in the right parieto-occipital region, where a large firm encapsulated endothelioma was seen growing from the falx cerebri and compressing the right hemisphere very markedly. This was completely removed, and found to weigh 135 grm. and measure 7 by 6·5 by 5 cm.

Upon her discharge from the hospital on August 6 the patient showed no signs or symptoms except the left hemianopia. She resumed her household duties and has remained well ever since.

Examination on June 25, 1926, showed a complete left homonymous hemianopia coming right to the fixation point.

Optic nystagmus.—Clockwise rotation of the drum produced a regular nystagmus of wide range and well sustained. The quick jerk carried the eyes to the right and slightly past the mid-position. Anti-clockwise rotation caused a slightly irregular nystagmus of wide range and well sustained. The quick movement carried the eyes from the mid-position far to the left; the patient seemed to be using the right fields of vision for fixation.

Case 21.—L. S., aged 27, was admitted under the care of Dr. Russell on January 28, 1924.

She had been for several months subject to left-sided epileptic attacks, which began in the tongue and affected the left side of her face and her left limbs in succession, and to attacks of severe headache. In March, 1924, a trephine opening was made and a tumour was found in the lower part of the right frontal lobe and the adjoining portion of the precentral gyrus. No attempt was made to remove it, but it was later treated by radiation.

On January 7, 1920, she was readmitted, as she was again subject to left-sided epileptic attacks; some of these commenced with spasms in her tongue, others with paræsthesiæ in the left side of the tongue and face.

Examination.—There was no paresis, sensory disturbance or change in her reflexes.

Vision.—Acuity was good. The fundi were normal and the visual fields were unrestricted.

Optic nystagmus.—Clockwise rotation of the drum elicited regular, rapid, and well-sustained nystagmus of large range to the right; anti-clockwise rotation produced identical nystagmus to the left.

Case 22.—A. C., aged 11, was admitted on October 8, 1925, under the care of Dr. Russell. He died on February 27, 1926.

At the age of 3 years he had a fall on the back of his head. When 5 years of age he had a right-sided otorrhœa lasting two months, which was followed by deafness. From this time he complained of headaches which had become more severe during the past year, and were then associated with vomiting and mistiness of vision.

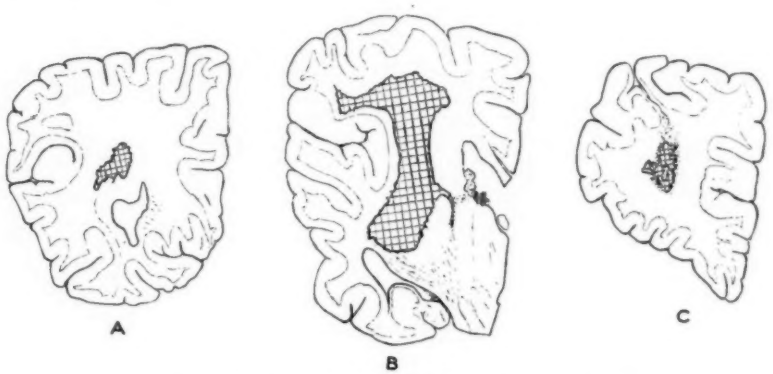


FIG. 12.—The position of the cyst is indicated by cross hatching.

Examination.—He was a bright, intelligent boy; no trace of aphasia or dysarthria. There was no paresis, sensory disturbance or change in the reflexes. Middle-ear deafness was present on the right side.

Vision.—Acuity was $\frac{6}{6}$ in each eye. There was marked bilateral papill-œdema, with macular fans and some choroido-retinitis in the periphery of the fundi. His visual fields were normal and there was no attention hemianopia.

Optic nystagmus.—Clockwise rotation of the drum evoked regular rapid nystagmus to the right, of medium range and well sustained. Anti-clockwise rotation elicited similar nystagmus to the left.

On January 15, 1926, a right-sided decompression was done to relieve pressure. The patient died six weeks later.

Autopsy.—The right hemisphere was swollen; in removing the brain a cyst that came near to the surface was ruptured in the right second frontal convolution. When the brain was examined after hardening, the cyst was seen to extend from $2\frac{1}{2}$ cm. behind the frontal lobe to within 6 cm. of the occipital pole. In the frontal lobe it lay dorsal and lateral to the anterior horn of the ventricle

(fig. 12, A). In a coronal section at the anterior commissure there was a large cavity which included the dorsal and lateral part of the caudate nucleus and the fibres passing to the anterior limb of the internal capsule. A narrow projection from it passed along the lateral aspect of the lenticular nucleus towards the region of the nucleus amygdala. At the level of the middle of the thalamus there was an irregular cavity, 6 cm. in height and 1½ cm. in breadth, which occupied the whole central white matter of the hemisphere except the subcortical fibres (fig. 12, B). It affected the upper and lateral part of the lenticular nucleus, and a second slit projected from it between the lenticular nucleus and the internal capsule. The internal capsule was not affected. In the posterior part of the hemisphere the cyst continued in the central white matter, unconnected with the ventricle; in the occipital pole it lay dorsal to the posterior horn of the ventricle and did not at any level involve the optic radiations (fig. 12, C). Microscopical examination of the cyst revealed only normal tissue bounded by a narrow layer of sclerosed neuroglia: there was no evidence of tumour or new growth.

Certain points of interest arise from consideration of these and other cases in which optic nystagmus was unaffected by large cerebral lesions. In the first place it should be noted that in many patients the lesions were stationary and of long standing, as in Cases 5, 20, and 22, or the lesion was a slow-growing endothelioma which compressed rather than invaded the brain, although in Case 20 it had produced a hemianopia, and in another patient (not reported in detail) a severe degree of hemiplegia. The influence of the site of lesion in this group of cases will be discussed later.

Brief reference must be made to the data we obtained in the study of the cases with definite evidence of cerebral disease, the location of which was verified by neither operation nor post-mortem examination. Sixteen of these patients suffered with hemiplegia due to vascular disease, many of whom had disturbance of sensation as well on the affected side. Of these sixteen cases, seven revealed a normal and equal nystagmus to rotation of the drum; five showed a slight but definite impairment of the response to the one side; while in four cases there was a very feeble, or complete loss of, optic nystagmus when the drum was rotated toward the side of the cerebral lesion. Of the two patients with hemianopia, one had a normal response, the other showed a loss of nystagmus to the hemianopic side.

According to Cords, Wernoe found absence of optic nystagmus to the right in eleven out of twelve aphasic patients, while in nine patients with motor aphasia Cords elicited no nystagmus to the right in one, no nystagmus to either side in four, and in the remaining four a normal response. Nine of our cases with vascular lesions had some degree of

aphasia. In two the nystagmus was normal and equal to the two sides, in three there was slight impairment to clockwise rotation of the drum, in three others the response to the right was feeble, and in one it was lost. We can therefore not correlate a disturbance of optic nystagmus with any form of aphasia.

In nineteen patients the clinical findings pointed definitely to cerebral tumour with increase of intracranial pressure. Of these, seven had normal and equal nystagmus to rotation of the drum to the right and left, five showed an irregular type of response in which there was no contrast between the two directions of rotation, while in the remaining seven cases there was a feeble or absent response to the one side. We are unwilling to draw any conclusions regarding the localizing value of the disturbance of the nystagmus in this group of unverified cases, other than to point out that when the response was disturbed the loss was always to rotation of the drum towards the side of the cerebral lesion.

One important point which comes out in the investigation of our cases is that in some, in which the lesions were stationary and of very long standing, no disturbance of optic nystagmus was present, though in other cases more acute lesions in the same region of the brain did abolish it. In Case 20, for instance, a hemianopia had existed since an operation two years previously, and in Case 5 a gunshot wound, inflicted in 1918, had produced an injury from which we would have expected to see loss of nystagmus result. Further, in Case 22, optic nystagmus was undisturbed, although an enormous cyst, which was evidently of long standing, occupied the central white matter of the greater part of the one hemisphere. It consequently seems probable that disturbances of optic nystagmus may disappear in the course of time, providing the lesion is stationary, and that the cortical activity concerned in it may be slowly readjusted as to make possible the production of a normal response. Further investigations on this point will, however, be necessary, especially re-examination at intervals of patients in whom optic nystagmus is at present absent.

(3) Influence of Lesions of the Brain-stem and of the Cerebellum, and of Existing Spontaneous Nystagmus.

It seemed interesting to observe the effect on optic nystagmus of lesions of the brain-stem, especially those that interfered with conjugate movements of the eyes, and the influence of pre-existing nystagmus of various types.

We have been able to examine three cases in which conjugate lateral

movements of the eyes were affected to one or both sides; the lesion was confirmed by autopsy in only one of these, but the nature of the symptoms in the remaining two cases can leave no doubt as to the approximate site of the lesion.

Case 23.—J. A., aged 26, was admitted under the care of Dr. Adie, February 2, 1926. Died May 1, 1926.

He had headaches and difficulty in walking since September 1925. Soon afterwards he complained of double vision and weakness of his left side. Speech became slurred in December, and difficulty in swallowing, with a tendency to nasal regurgitation, developed.

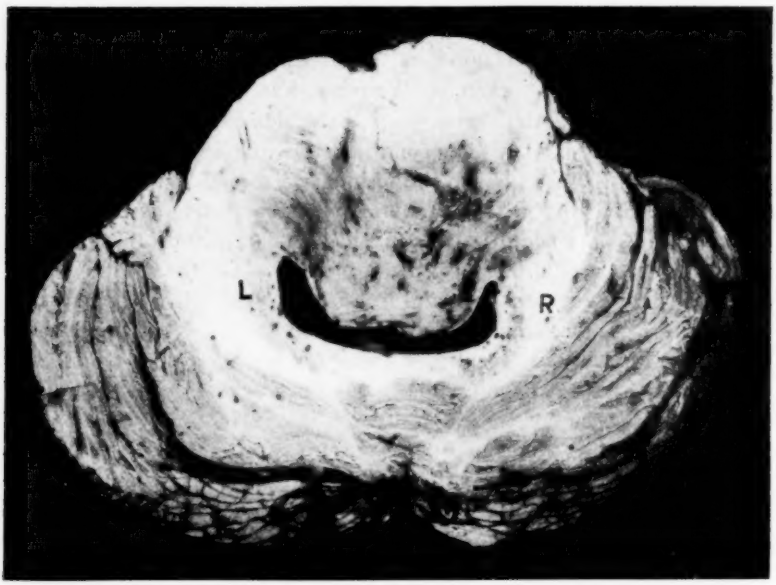


FIG. 13.

Examination.—The patient presented the picture of a bulbar palsy, with dysphagia and marked dysarthria. There was diminished sensation on the left side of the face, and left facial weakness. He also had a general left hypo-æsthesia and hemiparesis. On the right side there was decrease in tone, with action tremor and inco-ordination. The ocular movements to the right and left were defective and a coarse irregular nystagmus developed when they were attempted. To the left there was a practically complete conjugate palsy, but on right deviation the left eye moved in quite well. Upward and downward movements and convergence were normal. The pupils were unequal, and their reactions were sluggish.

Vision.—Acuity was $\frac{6}{18}$ in each eye. The fields were full. The fundi were normal.

Optic nystagmus.—Clockwise: no response. Anti-clockwise: an occasional jerk to the left, but frequently no movement occurred.

While in the hospital the patient developed hyperæsthesia to pain on the left side. He died on May 1.

Autopsy.—There was a great bulbous enlargement of the whole of the pons, with excrescences of tumour burying the basilar artery in the central furrow. Cross-section at the level of the exit of the fifth nerve showed a diffuse infiltration of the whole of the tegmentum, with projection into the fourth ventricle. The right side of the pons was involved more than the left, and the median raphé displaced far to the left (fig. 13). Microscopical sections showed that the glioma extended up to the ventral and posterior part of the thalamus on the right side, but only as far as the red nucleus on the left side. Caudalward the tumour infiltrated the medulla for a short distance only.

Case 24.—A. O., aged 36, was admitted under the care of Dr. Walshe, December 2, 1925. He complained of headache, and developed gradually increasing palsies of the cranial nerves on the left side.

Examination.—There was a paresis of the fifth, seventh and eighth cranial nerves on the left side. He was unable to deviate his eyes to the left, but the other ocular movements were full. A slow horizontal nystagmus developed when he attempted to look to the left, a more rapid nystagmus on deviating to the right and on looking upwards. He had also left-sided cerebellar symptoms.

Optic nystagmus.—The responses obtained on rotation of the drum on its vertical axis were inconstant and irregular. At times no nystagmus whatever could be obtained, especially on anti-clockwise rotation. At other times an irregular nystagmus resulted, the most striking feature of which was the oblique direction of the jerks, especially in the left eye, in which the movements were practically vertical.

Case 25.—W. B., aged 45, has been under the care of one of us for the past two years. His illness began with diplopia which has persisted.

Examination on numerous occasions revealed the same condition: there have been slight right-sided cerebellar symptoms with difficulty in walking, but his reflexes and sensation are normal. The functions of his cranial nerves, except the ocular movements, are unaffected. Visual acuity is $\frac{6}{6}$ in each eye when corrected, and his visual fields and fundi are natural.

When he was first seen he was unable to move his eyes to the right to order, or to turn them to an object in the right halves of his visual fields. On the request to look to the left, or to gaze at an object to his left, he blinked and shook his head, but succeeded in deviating his eyes to this side only after seven to ten seconds. If, however, he was asked to follow with his eyes an object moving slowly to either side, his eyes deviated quickly and naturally; and if, while he continued to gaze at an object, his head was rotated passively,

his eyes remained fixed on the object, that is, they deviated to the side opposite to that towards which his head was moved. When, by either of these devices, his eyes were brought into the lateral conjugate position, he had great difficulty in bringing them into the central position again; he usually did so only by closing his eyes and shaking his head. It was sometimes possible to obtain a deviation of his eyes to one side by making a loud noise to that side. Convergence, the vertical ocular movements and the pupillary reactions were normal.

Labyrinthine tests.—The right ear was irrigated with water at 26° C. for two and a half minutes, 600 c.c. being used. During the irrigation the patient was quite comfortable; there was no vertigo, nystagmus or deviation of the eyes, but his outstretched arms deviated to the right. When, however, the irrigation ceased, the eyes turned almost immediately to the right, and remained fixed in this position for two to three minutes; he was unable to move them by will to the central position, and even when his head was rotated abruptly to the right, or when he was asked to follow a slowly-moving finger to the left, his eyes did not return immediately to their normal position. A similar result was obtained by irrigation of the left ear with cold water. Passing a galvanic current through his head, the positive pole being in his right ear, produced an inclination of his head, and later of his trunk, to the right, and an incomplete deviation of his eyes to the left: nystagmus did not develop. When the positive pole was on his left ear his eyes did not move.

The patient has improved, but he has not regained the power of natural voluntary movement to either side, that to the right is still incomplete, and to the left it is effected only very slowly and with great difficulty.

Optic nystagmus.—Clockwise rotation of the drum produced an extreme deviation of his eyes to the left, in which position they remained fixed for several seconds. The patient complained of great discomfort, "as if his eyes were being torn out of his head." No nystagmus was observed. Anti-clockwise rotation evoked a similar extreme deviation of his eyes to the right, accompanied by intense discomfort. Vertical nystagmus was easily elicited by rotation of the drum on a horizontal axis.

In this complicated case, in which there is most probably a lesion in the pons, the power of voluntary lateral deviation of the eyes was severely affected, and the nystagmus that normally results from labyrinthine stimulation was lost; a lateral deviation of the eyes could be, however, obtained by caloric stimulation and in response to certain visual and acoustic stimuli. The quick phase of optic nystagmus was also abolished. This may be due to interruption of the cortico-bulbar paths that effect voluntary deviation of the eyes.

Magnus has shown that nystagmus may be elicited by rotation of an animal and by caloric stimulation of the labyrinth, even after transection of the brain-stem caudal to the trochlear nucleus, and that con-

sequently the fore-brain, or a supranuclear centre, is not necessary for the quick phase, as has been assumed. Though this be true for rotatory and caloric nystagmus, it cannot hold for optic nystagmus, which we have frequently found abolished by lesions limited to the fore-brain.

These three cases show that lesions which disturb voluntary lateral deviation of the eyes may abolish optic nystagmus. In Cases 23 and 24, in which lateral conjugate movements of the eyes to all stimuli were absent or diminished, probably owing to damage of the lowest level mechanisms that effect them, little or no response could be obtained, while in Case 25, where the lesion probably lay at a higher level and only interrupted certain connections of these mechanisms, and especially those that subserve voluntary movement, the slow phase was present but the rapid phase absent.

We have also investigated two cases with local cerebellar lesions due to the removal of tumours, and three cases of acoustic nerve tumour. All these five patients had spontaneous nystagmus on lateral movement of the eyes, and in each it was slower and coarser on deviation of the eyes toward the side of the lesion. Optic nystagmus was easily obtained in all these patients, but was slower in rate and wider in amplitude toward the side of the lesion than to the opposite side; in some of the cases it was more irregular and sometimes ceased for a moment. In one case the jerks were so slow that the finer and more rapid spontaneous rotary nystagmus could be observed in the intervals between the jerks evoked by rotation of the drum. This difference between the optic nystagmus to the right and left may be due to the greater difficulty, either apparent or latent, which patients with large and especially acute unilateral cerebellar lesions have in deviating their eyes towards the side of the lesion.

One case of congenital nystagmus was also examined in which both on forward fixation of the eyes and on deviation in all directions a slow pendular nystagmus existed. Clockwise and anti-clockwise rotation of the drum simply exaggerated the nystagmus present on forward fixation; the nystagmus became wider in amplitude and faster in rate, but the pendular character of the oscillations persisted, the swing being equal and identical in both directions. Bárány and Brunner have described in cases of spontaneous nystagmus of non-labyrinthine origin an inversion of the response; instead of the typical nystagmus occurring in the direction opposite to that of the drum, no nystagmus developed, or the rapid jerks occurred in the direction of the rotation.

Discussion.

A review of the results we have obtained from the examination of numerous cases shows that, in the first place, disturbances of vision as such do not interfere with or abolish optic nystagmus, provided the patient has even the vaguest perception of the figures or lines on the rotating drum. This is true in cases where the blindness is due to lesions of the optic nerves, of the chiasma, of one optic tract, or of the optic radiations. Even central fixation is not necessary, provided that sufficient visual perception remains in any other portion of the field; in other words optic nystagmus can be elicited even when the patient can rely only on extramacular vision. Further, we have repeatedly obtained normal nystagmus in cases of homonymous hemianopia. There can be no doubt that Bárány's conclusion that in hemianopia the quick phase is absent to the blind side is incorrect, or that loss of optic nystagmus to the blind side results directly from the visual defect. It is true that in many hemianopic patients it is not possible to elicit nystagmus to the non-seeing side, but this must be due to some other cause than the blindness itself.

Strauss has correlated loss of optic nystagmus to the one side with disturbances of visual attention to this side. By visual inattention we mean the condition which one of us studied with Head in 1911, and of which we published several examples seen in gunshot injuries of the brain during the war. It is a condition in which there is not necessarily any loss in the fields of vision, or diminution of visual perception in any portion of the fields, but when two objects are simultaneously presented to the patient, on different sides of the fixation point and at such a distance from it that they make equal angles with the visual axes, the patient perceives the object to the one side only, or in a series of tests frequently fails to perceive the object on one side. This condition is attributed to a failure of local visual attention to the side opposite the cerebral lesion. It is frequently found associated with lesions in the region of the angular gyrus. In some of our cases visual attention was certainly defective to the one side, but we have had four in which clinical tests showed a marked defect of visual attention to the right or left, and yet the nystagmus could be elicited to both sides. On the other hand, we have observed cases in which optic nystagmus to the one side was lost, and yet visual attention was normal in both halves of the fields. We must consequently conclude that visual inattention in itself is not the immediate cause of loss of nystagmus.

We may assume that in following a moving object the patient employs macular vision, or, if this is impossible owing to the presence of a central scotoma, that part of the field nearest to the border of the scotoma by which the object can be perceived. In some of our cases with hemianopia coming to the fixation point, or with scotomata, it was impossible when the drum was revolving towards the seeing portion of the field, that the object following that on which the patient's gaze was directed could stimulate a seeing portion of the retina. Consequently Bárány's view that the quick phase is due to a glance at the succeeding line or figure must be incorrect.

We do not wish to enter into a discussion here on the nature of optic nystagmus, but the view put forward by Stenvers seems to us nearest the truth. According to this, optic nystagmus is a cerebral reflex with a centripetal centre in the occipital lobe, and a centrifugal centre in the frontal lobe, these two centres being connected by a reflex path. An interruption of this long reflex path, or of one of the centres, is the simplest explanation of the fact that the nystagmus may be abolished to the one side by lesions so variously situated in the brain. Our observations suggest that the occipital lobe is concerned in it, for all lesions of this region disturbed nystagmus: we cannot, however, provide definite evidence of the existence of a frontal centre.

Localizing Value of Optic Nystagmus.

Our main object in undertaking this investigation was to determine whether in optic nystagmus we have a test that would prove useful in helping to localize cerebral lesions, such as tumours and abscesses. We must consequently review our observations now and attempt to decide where in the brain a lesion must lie to disturb the nystagmus, and where disease may exist without affecting it.

Although we have been able to investigate a considerable number of cases in which the positions of the cerebral lesions were verified by autopsy or operation, we cannot claim to give a final answer to these questions, but our material will at least prove useful in the further investigation that this matter deserves. In attempting to determine the localizing value of optic nystagmus we meet grave difficulties. In the first place many of the lesions were large, and consequently involved such extensive portions of the brain that it is from any one of them alone impossible to decide as to disturbance of what part the symptoms were due. In the second place, more than one lesion to

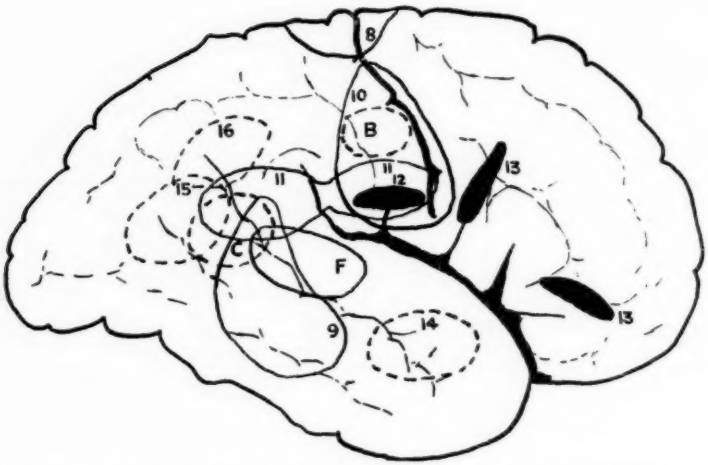


FIG. 14.—The projection on the lateral surface of the brain of lesions that disturbed optic nystagmus. Those verified by post-mortem examination are marked by a continuous line, and those determined by operation by a broken line. Operative incisions are indicated in black. The numbers refer to the number of the recorded cases in the paper, the letters to unpublished cases.

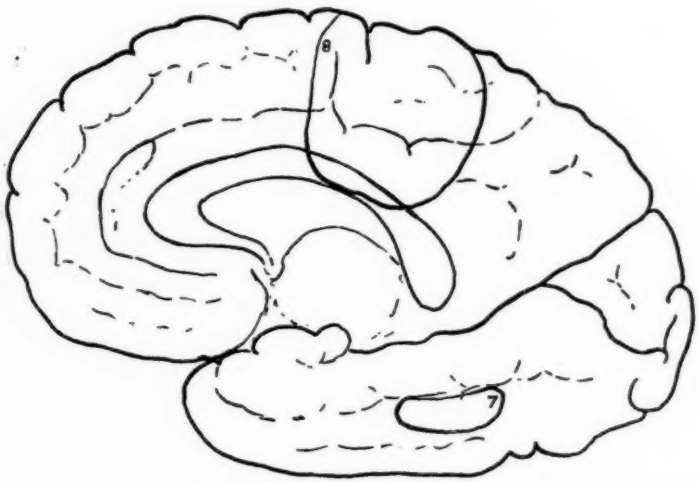


FIG. 15.—Legends as in fig. 14.

which the absence of nystagmus could be attributed existed in some cases, as in Cases 11 and 13. In the third place, as we have pointed out, there is evidence that nystagmus to one side which had been abolished or affected by a local lesion may in time return to normal. Finally, in most of our cases the lesions were tumours which infiltrated the brain widely, though they did not necessarily abolish the functions of all the parts they involved, and on the other hand they exerted diffuse pressure on neighbouring tracts and portions of the grey matter.

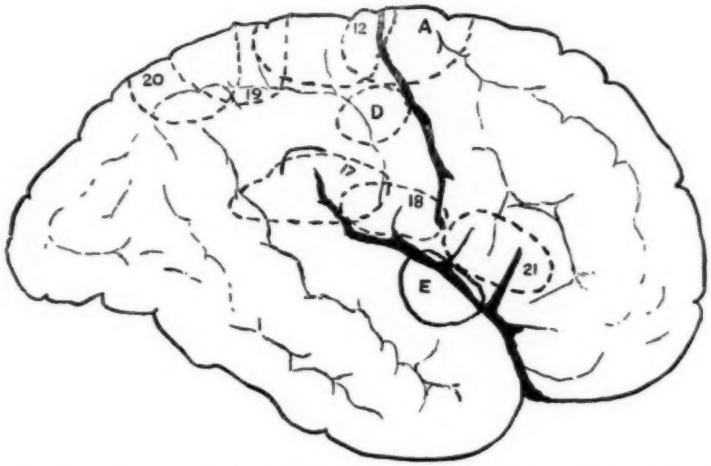


FIG. 16.—Projection on to the lateral surface of a brain of lesions that did not disturb optic nystagmus. Legends as in fig. 14.

In figs. 14 and 15 we have projected on the lateral and mesial surfaces of a right hemisphere the lesions which did in our verified cases affect lateral optic nystagmus; unfortunately we have not sufficient observations to justify any statement with regard to loss of vertical nystagmus. In fig. 16 we have indicated similarly the positions occupied by lesions that did not disturb the nystagmus. This method can only give an approximate idea of the local values of lesions, but it will at least facilitate discussion.

It will be seen that our observations include no case of disease of the visual cortex or even of parts adjacent to it, and that by a curious chance lesions of the frontal lobe are represented only by two operative

incisions (Case 13) and by one tumour seen at operation but not removed (Case 21).

One definite statement at least can be made, that a unilateral lesion of the fore-brain can disturb lateral optic nystagmus to the opposite only. If the lesion lies in the right hemisphere clockwise rotation of the drum evokes a nystagmus consisting of slow deviations of the eyes to the left and quick jerks to the right, in other words a nystagmus to the right: but anti-clockwise rotation has no effect, or produces a less regular or less pronounced nystagmus to the left.

On inspecting fig. 14 it is seen that a large proportion of the lesions that abolished nystagmus lay in the inferior part of the parietal lobe and in the temporal lobe. Further, those in the temporal lobe lay in its posterior part, with the exception of Case 14, in which, according to the surgical notes, the tumour was removed "from near the apex of the temporal lobe," but the existence of hemianopia and of severe sensory disturbances indicate that it probably lay more posteriorly, perhaps nearer to the supramarginal gyrus. In Case 7 the tumour was found in the basal surface of the temporal lobe, but it extended upwards through the white matter. As the incision through the white matter under the lower part of the postcentral gyrus in Case 12 abolished nystagmus which was present before the operation, this region of the brain must be also included in the area concerned with nystagmus.

The only frontal lesions which affected nystagmus were in Case 13, in which there were two operative incisions, one in the anterior part of the third frontal convolution and a second in the posterior ends of the second and third frontal gyri. It seems probable that the latter was the cause of the loss, as in Case 21 a tumour in the third frontal gyrus had no effect on the nystagmus. In Case 8 the tumour lay chiefly in the mesial part of the hemisphere, but it extended into the central white matter, almost down to the level of the fissure of Sylvius (fig. 7).

On turning to fig. 16 we find a series of lesions near the apex of the hemisphere, none of which disturbed nystagmus. It is true that Cases 19, 20 and A were endotheliomata which merely compressed the brain, but in Case 20 there was a permanent hemianopia and in A a severe hemiplegia. In Case 12 a glioma infiltrated this region, and in Case D a glioma had been removed. In Case E an endothelioma growing within the fissure of Sylvius merely compressed the first temporal and the inferior frontal gyri. In Case 17 nystagmus to the opposite side was represented before operation by a few irregular jerks only, but we have included it among the negative cases, as the nystagmus was equal

to the two sides three weeks after the operation and in subsequent examinations. In Case 18 a tumour was removed from the lower end of the fissure of Rolando.

To any conclusion we can draw some of our cases present obvious exceptions. It seems, however, that nystagmus to the opposite side is affected when a lesion lies in the supramarginal or angular gyrus, in the adjacent portion of the parietal and temporal lobes, in the posterior end of the second frontal convolution or along a line joining this with the angular gyrus.

Our observations consequently tend to support Stenvers' hypothesis, that reflex centres for optic nystagmus lie in the occipital lobe and in the second frontal convolution, and that these are connected by a reflex path which runs through the white matter of the hemisphere.

REFERENCES.

[1] Bárány, B. *Arch. f. Augenheilk.*, 1921, **88**, 139.
[2] Brunner, H. *Klin. Monatsbl. f. Augenheilk.*, 1922, **68**, 783.
[3] Cords, R. *Deutsch. Zeitschr. f. Nervenheilk.*, 1925, **84**, 152.
[4] Ohm, J. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1926, **102**, 444.
[5] Stenvers, H. W. *Psychiatr. en Neurolog. bladen.*, 1925.
[6] *Idem. Schweiz. Arch. f. Neurol. u. Psychiatr.*, 1924, **8**, 279.
[7] *Idem. Acta Oto-laryngologica*, 1925, **8**, 545.
[8] Strauss, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1925, **98**, 93.

AN EXPLANATION OF THE TWO-STAGE RECOVERY OF SENSATION DURING REGENERATION OF A PERIPHERAL NERVE.

BY JOHN S. B. STOPFORD, M.D.
Professor of Anatomy, University of Manchester.

Introduction.

The important observations which were made in the classical experiment upon Head's own hand, both immediately after division of the radial and musculo-cutaneous nerves in the region of the elbow, and during the regeneration of these nerves, pointed clearly to the conclusion that cutaneous sensation must be divided into two systems. The way in which one group of elements of sensation may be dissociated from the other, either one or the other being retained—the recovery in two stages of cutaneous sensation after the successful suture of a peripheral nerve—and the striking and distinctive characteristics of the two stages—appear to me to offer no other satisfactory interpretation of the clinical observations. Nevertheless, the existence of two systems in cutaneous sensation has been denied by some, and a number of explanations of the observed facts have been submitted. Although several of these criticisms of Head's views have been reviewed previously, it seems necessary to consider briefly some of them before attempting to explain how my own investigations of deep sensibility support Head's hypothesis, and suggest a simple explanation for the observations made upon both cutaneous and deep sensibility.

(1) It has been suggested that the early return of protopathic sensibility may be explained by nerve overlap, and about five years ago Pollock [4] attempted to revive this view, particularly with reference to the early recovery of the ability to appreciate the pain induced by the prick of a sharp instrument like a needle. Regular systematic examinations of patients over long periods, as long as ten years in some of my own cases, have proved that the extent of the loss of the protopathic sensibility does not become reduced appreciably if regeneration cannot occur, as in patients who have suffered the destruction of such a considerable length of the nerve that suture is impracticable. Further-

more, it must be pointed out that the conception of two distinct systems in cutaneous sensation does not depend solely upon the dissociation found during recovery. Immediately after the operation upon Head's own arm, two complementary forms of dissociation were present: (*a*) At the periphery of the field of sensory loss, epicritic sensibility was lost and protopathic retained, and (*b*) in "the triangle" protopathic sensibility was lost and epicritic retained. Both these forms of dissociation are encountered from time to time in the examination of patients after the division of a peripheral nerve, and when kept under continuous observation during the period of recovery they both behave in the manner described by Head, which is only consistent with the presence of two distinct and independent systems.

(2) In another explanation of the protopathic stage of recovery it is inferred that the conditions are dependent upon incomplete and imperfect regeneration of the nerve-fibres, which causes them to function less precisely. If the fibre permits the passage of an impulse when its peripheral termination receives an adequate stimulus, any change in consciousness must be dependent upon the central terminations of the path which are undisturbed by any injury to, and subsequent operation upon, a peripheral nerve. It is impossible to believe that this state of incomplete repair could persist indefinitely, and yet this would be necessary if we are to accept it as the explanation of the protopathic stage, since it is not very uncommon after secondary suture of a nerve to find recovery arrested and a large area of skin exhibiting only protopathic sensibility with its characteristic accompaniments for an indefinite time. A greater objection to this explanation is that it fails to throw any light on the normal sensory condition of the glans penis. Head has proved that the sensation in this region shows exactly the same characteristics and peculiarities as an area of skin in any part of the body at the end of the first stage of recovery, and there appears to be no doubt that the glans penis is endowed with protopathic and deep sensibility only. Since this is the normal condition in the glans penis, it is not possible to introduce as an explanation of its existence an abnormal physiological state of the nerve-fibres, and it appears reasonable to suppose that the same explanation will hold good for the normal sensory condition of the glans penis and the sensory state of the skin at the end of the first stage of regeneration of a peripheral nerve. A further objection to this explanation is afforded by Head's experiment of rapidly cooling the hand during the final stages of recovery, when it was found that the affected area exhibited the old characteristics and

was *thrown back* into a protopathic condition, although before cooling the recovery of epicritic sensibility could be demonstrated by tests, and such characteristics of the first stage as referred sensations were absent. I have been able to verify this experiment on a number of occasions during the last few years, and feel that it provides very strong evidence in support of the presence of two distinct systems in cutaneous sensibility. A somewhat similar explanation of the protopathic stage has been offered, which suggests that the conditions found are due to incomplete repair of the end-organ rather than the fibre. It appears unnecessary to discuss this in any detail, since practically all the criticisms advanced with regard to incomplete regeneration of the nerve-fibres holds good for this further suggestion. Imperfect repair of end-organs cannot account for the normal sensation of the glans penis, nor is likely to be the reason for the indefinite persistence of the protopathic stage in some cases of secondary nerve suture, and it fails to explain satisfactorily the reproduction of the phenomena of the first stage of recovery by cooling.

(3) Some, whilst prepared to admit the existence of the two systems, have held the view that the two-stage recovery is dependent upon a difference in the rate of growth or regeneration of the protopathic and epicritic fibres. Probably the simplest explanation of the observed facts would be that the protopathic fibres grow down to their end-organs at a more rapid rate than the epicritic, and this was for a time rendered even more attractive by the suggestion that the protopathic fibres were unmyelinated [5].

(4) Subsequent histological and experimental researches have shown, however, that it is highly improbable that there is any structural difference in the epicritic and protopathic fibres. All the evidence at present available seems to indicate that nerve-fibres regenerating under identical conditions grow at the same rate. This has been demonstrated by histological examinations of regenerating nerves, both in experimental work upon animals and in nerves excised for various reasons after operations upon the human subject. Clinical observations in uncomplicated cases also constantly show that, after the successful suture of a nerve, voluntary action appears in the muscles about the same time as the recovery of protopathic sensibility in the skin equally distant from the line of suture. There seems to be little or no support for the contention that protopathic fibres regenerate more rapidly than epicritic, and all the evidence at present available opposes such a view; consequently we must endeavour to find a more reasonable and

acceptable explanation for the two-stage recovery of sensation and the presence of two distinct systems in cutaneous sensibility.

Subdivision of the Sensory Loss after Division of a Peripheral Nerve.

In an earlier paper [9] I submitted evidence in support of the opinion that it was necessary to subdivide deep sensibility into two systems, just as Head had similarly subdivided cutaneous sensibility. The observations in support of this contention were made upon patients exhibiting defects of deep sensibility after division of a peripheral nerve and during the regeneration succeeding secondary nerve suture. In the period of regeneration it was found that two elements of sensation, the mere recognition of the contact of pressure and the pain induced by excessive pressure, recovered at an earlier date and more perfectly than the other elements included in deep sensibility—the accurate localization of a pressure stimulus, the appreciation of posture, and the range and direction of the passive movement of a joint. The former elements of sensation returned whilst protopathic sensibility was recovering, and usually proceeded to a complete recovery, as far as could be determined by the customary tests, whereas no change was discovered in the latter elements even in the most successful cases until a much longer time had elapsed after the nerve suture; in no patient was a complete recovery found even many years after secondary nerve suture. Observations made after primary nerve suture have demonstrated the same two stages in recovery, but the extent of the recovery of the power to localize accurately a pressure stimulus and appreciate the passive movement of a joint, has been much greater and more perfect than was ever the case after secondary suture. In a small proportion of cases, primary nerve suture was followed by a perfect and complete recovery of cutaneous and deep sensibility, but in my experience this is not common even under the most favourable surgical conditions. In the examination of a very large number of patients for long periods after both primary and secondary nerve suture, I have found these two stages in the recovery of deep sensibility to be present constantly, provided the operation leads to adequate regeneration, and I have noticed certain striking and significant similarities in the two systems of cutaneous and of deep sensibility.

(1) One system in each recovers after suture at an earlier date, and the recovery is more constant and much more complete than in the later systems. The time of the appearance of the earliest evidence of

recovery is very variable after secondary suture, even after allowing for the differences in level of the suture, but at approximately the same time changes are found in the earlier systems of both cutaneous and deep sensibility. In the case of primary suture the first evidences of recovery occur at a much more constant time both in skin and the deeper tissue. As a general rule, under favourable conditions the first signs of recovery of sensation appear about the same time as the reappearance of voluntary action or faradic response in the muscles at about the same level as the area of sensory loss.

(2) One system in each manifests evidence of recovery after suture at a much later date, and the recovery is less constant in occurrence and usually much less complete than in the other systems. The date after operation of the first signs of recovery is very variable after secondary suture, but rather less variable after primary suture; in my own experiences it is quite impossible to offer regular dates at which the various systems begin to recover even after primary suture. In a few patients, after secondary suture, no recovery of the later system in either cutaneous or deep sensibility is found, but some recovery is almost the rule if regeneration follows primary suture. In the former cases, if the earlier systems have recovered, the affected region will continue to exhibit the well-known "protopathic" qualities for years, or indefinitely. Signs of recovery may be discovered in the later system, both in skin and subcutaneous tissues, before the recovery of the earlier systems is complete, but in most patients after secondary suture its recovery is not manifested until a considerable time after the recovery of the earlier system has reached finality.

(3) At the end of the first stage of recovery after suture of a peripheral nerve—i.e., after recovery of the earlier system in both cutaneous and deep sensibility—the condition found bears a remarkable resemblance to that present after a lesion of the sensory cortex. Omitting for the moment the elements of sensation which have recovered and which will be referred to in the next paragraph, the most striking feature is the character of the response to pain, heat and cold. The abnormal vividness of the response, or the "intensification," as Head has described it, is familiar to all who have examined patients during the second stage of recovery after peripheral nerve suture, or one suffering from a destructive lesion of the sensory cortex which leaves the optic thalamus intact although isolated from the postcentral cortex. In both circumstances the patients use the same terms, and as far as it is possible to understand from their descriptions, appreciate the same experiences

when stimulated by a sharp pin, heat, cold, or excessive pressure. The excessive reaction and the characteristic radiation are so very similar in the two conditions that, to anyone familiar with the manifestations of lesions of the sensory cortex, the cortex and optic thalamus must be suggested constantly while making observations upon patients at the end of the first stage of regeneration after suture of a peripheral nerve. The indefinite persistence of these characteristics in all cases if no further recovery occurs must exclude, as Head has pointed out, the possibility of hypothetical irritation or imperfect repair as being responsible for the phenomenon. The cessation of the excessive reaction and the radiation on the return of the higher forms of sensation is equally significant and important, as is also its temporary reproduction under such circumstances as cooling of the part.

(4) Protopathic sensation and the system in deep sensibility which recovers earlier consist of cruder elements of sensation than those composing epicritic and the system in deep sensibility which recovers later and less perfectly. A more careful analysis of the elements of sensation in the four systems, in the light of Head's researches upon the sensory cortex [2], cannot fail to suggest that at the periphery, both in cutaneous and deep sensibility, we have to consider cortical and thalamic aspects of sensation. To do so is really only to apply sound physiological principles to the problems of peripheral sensation, since ultimately we must of necessity turn to the sensory cerebral centres for any explanation of the changes in consciousness induced by various stimuli. We find that the elements of sensation appearing in the two systems which recover late and which most frequently show imperfect recovery, or in a proportion of examples of secondary suture fail to exhibit any recovery, are those which Head has shown to have cortical representation; whilst the elements of sensation included in the two systems which recover early, more constantly and more completely are those which may be expected to exist after destruction of the sensory cortex. The likeness of protopathic sensibility and thalamic over-reaction have been referred to by Head, and my own researches indicate a similar likeness as regards the first stage of recovery of deep sensibility and uncontrolled thalamic functioning, and a careful consideration leads to the conclusion that the characteristics of the first stage of recovery in both cutaneous and deep sensibility are due to release of the thalamus from control of the cortex. All the observations recorded by both Head and myself support this view and seem incompatible with any other explanation which has been advanced. Strong support in

the light of Head's work on the sensory cortex is to be found in the changed responses which are discovered during the second stages of recovery of cutaneous and deep sensibility, and the return to the first stage by cooling of the part under investigation is very significant and important. On general grounds it seems only reasonable to expect to find an explanation of the two stages of recovery in the cerebral hemisphere, and such a view has the added attraction of illustrating once again that the functions of the nervous system are integrated on the principles of evolution.

The foregoing observations suggest the following classification of the elements of sensation affected by division of a peripheral nerve :—

I. Cutaneous Sensibility.	
Thalamic (early or more complete recovery), (protopathic of Head)	Discrimination of wider differences of temperature. Cutaneous pain
Cortical (late and less perfect recovery), (epicritic of Head)	Appreciation of lightest form of touch. Localization of lightest form of touch. Discrimination of finer differences of temperature. Recognition of two compass points, simultaneously applied, as two
II. Deep Sensibility.	
Thalamic (early or more complete recovery)	Appreciation of contact of pressure. Pressure pain
Cortical (late and less perfect recovery)	Recognition of passive movement of a joint. Accurate localization of pressure

Explanation of the Two-stage Recovery in both Cutaneous and Deep Sensibility.

If the thalamus and sensory cortex provide a reason for the two stages of recovery, it is possible to understand why a longer period must elapse before the fibres subserving the cortical forms of sensation function correctly than in the case of the fibres conducting impulses concerned with the thalamic aspects of sensation, as a very much more complex readjustment and re-education must occur after regeneration of the fibres in the former case than in the latter. We can appreciate also ample reasons for the more constant and perfect recovery of such aspects of sensation as cutaneous pain, pressure pain, and recognition of extremes of temperature, than for the higher forms such as those concerned with spatial recognition. However attractive such a central explanation may be, many people have experienced difficulty in understanding why, after degeneration and regeneration affecting only the peripheral sensory neurones, there should be such a profound upset of the cortical function. To explain this it is necessary to refer to the conditions now known to prevail in a peripheral nerve after suture.

Even in cases where there is no loss of nerve substance, as in some examples of primary suture, it is impracticable to procure perfect and accurate end-to-end apposition of the constituent nerve-bundles and avoid some disturbance of the intraneural pattern [11]. This postulates a grave limitation to the success of nerve suture, and is of the most serious consequence in secondary suture where a segment of the nerve has to be sacrificed and the intraneural anatomy inevitably and grossly disturbed. Recent researches upon intraneural plexuses and the arrangement of the bundles in the more important nerve-trunks demonstrate clearly what a serious practical difficulty this matter is, and also how excision of small segments of a nerve at many points in its course must render anything approaching accurate functional alignment absolutely impossible. In consequence of this inevitable disturbance of the intraneural pattern after suture, chance plays a considerable part in the success of the result, since a variable number of regenerating fibres must grow down into the endoneural, perineural or epineural connective tissues and be functionally lost, whilst others grow down heterogeneous peripheral fibres. I have submitted evidence [7] to show that afferent fibres may grow down to motor end-plates, and Boeke [1] has proved that motor-fibres of the central end do grow down sensory fibres in the peripheral end, and vice versa: and it seems probable that the inevitable disturbance of the intraneural pattern after nerve suture would exclude the possibility of any real functional recovery after secondary nerve suture in a high proportion of cases, if this was not compensated for to some extent by the very great increase in the number of young fibrils which grow out usually from the extremity of the central end. This probably permits a large proportion to be lost in the supporting tissue and by the crossing of afferent and efferent fibres. The greater disturbance of the intraneural anatomy of a nerve-trunk occurring after secondary suture is probably one of the most important causes for a less satisfactory functional recovery after this operation than after primary suture, and will in consequence have a significant and obvious bearing upon my observations on sensation after the two operations.

Since sensory fibres in the proximal segment are known to grow down motor paths in the distal, it is clear that there must also be a great disturbance of the sensory fibres themselves—i.e., fibres previously concerned with transmission of impulses excited by pain may grow down "heat"[1] paths, or "localization" paths, &c. The change in

[1] Such terms as "heat" and "pain" paths are used for convenience, it being understood that a heat fibre or path is one conducting an impulse, which on reaching the higher centres causes the sensation of heat.

consciousness depends upon integration within the central nervous system and the central terminations and connections of the fibres transmitting the impulses. These central connections are not disturbed by injuries to or operations upon the peripheral sensory neurones, but nevertheless the functioning of the cortex and thalamus may be seriously interfered with by the changes which are known to occur during the regeneration of a peripheral nerve after suture. If a "pain" fibre grows down a "pain" path in the distal segment and forms a connection with a regenerated end-organ which will respond to the stimulus of a pin-prick, there will be a normal path from the peripheral end-organ to the thalamus, and an adequate stimulus applied in the region of the end-organ will induce a sensation of pain immediately the pathway is anatomically complete. Similarly a "cold" fibre, or a "heat" fibre, having throughout undisturbed central connections, will permit normal function if, on regeneration, it forms a connection with a regenerated cold or heat end-organ, as the case may be. If, on the other hand, pain, cold, or heat fibres on regeneration join heterogeneous end-organs—excluding the question of threshold as we are only considering adequate stimuli—the quality of the stimulus required to induce an impulse in any given case will depend upon the end-organ, whereas the change in consciousness must alone have reference to the central connections of the path concerned. For example, a "pain" fibre growing down to a "cold" end-organ will transmit an impulse when the end-organ is stimulated by an adequate cold stimulus, but the patient will experience pain. For this experience of pain, as it is found during the first stage of recovery after suture of a peripheral nerve, it will not matter if a pain fibre, connected previously with an end-organ in the forearm, on regeneration is joined to one in the hand or a digit; all that is necessary for the typical all-or-nothing response is a protopathic end-organ and a pain path up to and including the thalamus. The anatomical connections between the peripheral end-organ and the thalamus are so simple that after suture and regeneration of a peripheral nerve, one might expect early (as soon as the necessary connections with the thalamus are made) recovery of the crude elements of sensation —as pain, heat and cold.

When we turn to the higher aspects of sensation we find the recovery of function much more complicated and the reason for the delay becomes apparent. To explain the principle it is easiest to refer to localization, but it can be applied to any of the higher aspects of cutaneous or deep sensibility. If a localization fibre, previously termi-

nating in the forearm, after regeneration grows down to a digit and reaches a tactile end-organ there, the adequate stimulus applied to that end-organ will not be localized accurately, and we should fail to find in the course of our clinical testing any evidence of recovery of the power to localize the point stimulated. We should probably make a note of a reference to the forearm in our records. It is conceivable that, after the lapse of time, a capable patient would by re-education overcome this and localize the stimulus more or less accurately. Such a period of re-education would explain the occurrence of an interval between the recovery of the crude forms and the higher forms of sensation. This principle, which is more easily cited and understood in the case of localization, may be applied to all the other elements of sensation included in the epicritic system, and for the recognition of the position of a joint, and shows how, in the higher aspects of sensation, even after homogeneous connections have been made, re-education is required before normal function is restored.[1]

There is an additional factor of great importance which implies a further reason for the less perfect recovery of the higher forms of sensation. As a result of the inevitable crossing of functionally distinct fibres—functionally distinct, of course, because of their central connections—after nerve suture, more paths concerned with the higher aspects of sensation are lost than is the case with pain, heat or cold. We have seen that in the latter a certain amount of heterogeneous crossing is possible without loss of function, but this is most probably not practicable for the former. We know little of the complex neural pattern upon which cortical functioning depends, but it would appear justifiable to say that heterogeneous connections of fibres concerned with the cortical aspects of sensation would result in loss of function. If a localization fibre on regeneration reaches an end-organ in the neighbourhood of an articulation, and is stimulated by movement of and concerned with the recognition of the position of that joint, it does not seem likely that by the most prolonged re-education the cortex is able to make any useful purpose of the information received by such a path from the periphery. Reflection will show that the same difficulty occurs whenever heterogeneous connections are made between paths conveying information from the peripheral end-organs to the cortex. Consequently it may be seen that disturbance of the intraneural pattern by nerve suture is likely to

[1] A little reflection will show that in many patients, even after the formation of homogeneous connections, re-education cannot be expected to restore normal functioning.

have a much more serious consequence upon the higher aspects of sensation, and offers reasons for the delay and less perfect recovery of them. We have previously noticed that the recovery is most imperfect when the risk of disturbance of the intraneural pattern is greatest, as in cases of secondary nerve suture.

To summarize the most important results of the inevitable consequences of suture of a peripheral nerve it may be said :—

(1) That heterogeneous connections within certain limits may be succeeded by recovery of the all-or-nothing response to pain, hot and cold stimuli. The adequate stimulus is dependent upon the type and condition of the end-organ, whilst the change in consciousness depends upon the central connections. Pain, heat and cold fibres reaching homogeneous end-organs in *any part* of the sensory field under investigation will function as soon as connections from end-organ to thalamus are re-formed in their full continuity.

(2) That heterogeneous connections in the case of fibres concerned with the higher aspects of sensation are not likely to be succeeded by any return of sensibility, either immediate or in the future. Fibres concerned with the higher aspects of sensation, such as spatial recognition in one, two or three dimensions, may reach homogeneous end-organs without any recovery of function that can be discovered even by graduated tests, but it seems possible under these circumstances that by re-education some recovery may follow at a later date. The extent of the recovery under such conditions not only depends upon fortuitous regeneration, but also upon the educability of the patient.

Such a survey of the results of suture offers both an explanation for the two stages in the recovery of cutaneous and deep sensibility, and in addition provides a reason for the less complete and perfect recovery of the higher forms of sensation. We are able also to appreciate a cause for the imperfection or absence of recovery of epicritic sensibility and the power to localize accurately the point stimulated, and the recognition of the position or movement of a joint after secondary suture, as after that operation we know that the disturbance of the intraneural pattern is inevitably much greater than after primary suture, and consequently there is an enhanced risk of heterogeneous connections being formed. Even after primary suture under ideal conditions, in my experience, the ultimate sensory recovery very rarely approaches that described in the classical experiment on Head's own arm. Since we are apt to compare all our results after nerve suture in the light of the information recorded by Head and Rivers, it is wise to enumerate the

probable reasons why the recovery of sensation was exceptionally complete in the original experiment.

(1) The operation was done under the most ideal conditions, all the possible causes for disturbance of the intraneural pattern being reduced to the minimum.

(2) Owing to the fact that in Head's hand the radial nerve was practically distributed solely to skin, which I have shown [8] to be an exceptional form of distribution, four elements of sensation were for practical purposes unaffected by the section of the nerve: pressure, pressure pain, localization of pressure, and recognition of position and passive movement of a joint. This would very materially reduce the risk of heterogeneous connections being made on regeneration, and would offer a second important reason for the very complete and perfect recovery of sensation.

(3) The greatest possible re-education would succeed regeneration.

Reflection on the part of those who have had opportunities of following the recovery of sensation in a number of patients after nerve suture will demonstrate how the views expressed in this paper shed light upon many of the otherwise mysterious and unintelligible findings which are from time to time encountered. It is unnecessary to refer to more than two examples to illustrate what is meant. I have found that, on testing pressure pain by means of the spring algometer, similar to that used by Rivers [3], by which the pressure required to induce pain is recorded in kilogrammes—in patients where the division of the nerve was in the distal part of the limb and there was no absolute sensory loss, the readings on the affected side *tended* to be definitely lower than on the sound side: whilst in patients previously manifesting a considerable disturbance of deep sensibility and examined during recovery, when there was a complete return of protopathic and the first stage of deep sensibility, the readings at all points on the affected side were *very markedly* lower than on the sound side. This was encountered even with digits that at the outset had exhibited an absolute sensory loss, or which originally had given a higher reading with the algometer. Such results baffled me for a long time, but I suggest that the explanation offered for the two stages of recovery seen during regeneration offers a reason. On account of the causes previously stated, it is probable that a number of pain fibres on regeneration may grow down to tactile end-organs. From the information gained from other workers upon sensation, using calibrated hairs, it appears clear that these end-organs will respond to different degrees of pressure, some to very slight,

some to medium, and others only to considerable pressure, but all will be excited by less pressure than that required to stimulate a pressure pain end-organ. The change in consciousness resulting from stimulation of these tactile end-organs now centrally connected by pain fibres will be the experience of pain, and thus we could easily obtain the extremely low (in fact not uncommonly so low that they are difficult to measure by the algometer) readings after regeneration. As a criticism of this, it may be pointed out that a similar condition may be found after division of a nerve at the wrist, succeeding which there is commonly no absolute loss of tactile sensibility. The absence of an absolute loss does not preclude the possibility of division of quite a large number of tactile fibres supplying the deeper tissues, and in previous communications [9 and 10] I have proved that in the hand deep sensibility is only in part subserved by fibres which run with muscular branches, and that the subcutaneous tissues of the hand are provided with many nerves which reach the hand by running in the main nerve trunks into the palm. Therefore it may be said that a study of the anatomy of deep sensibility does not afford any criticism of this explanation, but maintains that it is reasonable and possible.

As a second illustration it is worth referring to the strange and perplexing responses to various stimulations in the course of routine examinations of patients during regeneration after nerve suture. In my own experience they have been found most frequently when testing with a pressure stimulus. It has been found by no means rare to get replies to such a stimulus in the affected sensory field as the following: "It feels as if you were burning me with a match." "That was like an electric shock." "I felt you move my finger then." In ordinary routine examinations we are liable to pay little or no attention to such responses and to pass on to map out the extent of the sensory loss, yet to anyone studying sensation they are of real interest, and not to be dismissed or simply noted under the misleading term "paræsthesia." It has only been within the last few years that I have been able to offer any explanation of these occurrences, although their frequent appearance had for some time suggested that they probably had some important meaning. It appears to me now reasonable to believe that heterogeneous connections could be responsible for these responses, and it is not difficult to understand how "heat," "pain," and "posture" fibres growing down to tactile end-organs could explain respectively the three responses quoted above.

Clinical observations upon patients suffering from what has been

termed physiological division of a peripheral nerve are also of some interest with reference to the explanation offered in this paper of the two-stage recovery of both cutaneous and deep sensibility. By physiological division we mean a condition in which there is no anatomical division of the fibres, but the passage of the impulse is prevented by such things as compression from extraneural cicatricial tissue, bone, or callus. Many patients suffering from such a condition were encountered during the war, and in a few I had an opportunity of seeing the compression develop and ultimately obstruct completely the passage of nerve impulses through the constituent fibres, as well as the sequence of events after release of the nerve from compression. If the extraneural fibrous tissue which is causing the compression is surgically removed, the nerve replaced in a new bed where it is surrounded by undamaged tissues, and the case is uncomplicated by the presence of intraneural fibrosis—an excellent recovery of function and sensation is to be expected. The recovery of sensation, however, does not follow the two-stage method always seen after nerve suture when, of course, anatomical division of the nerve has occurred. After successful neurolysis in uncomplicated cases of compression the recovery of sensation is first to be seen in the proximal part of the field of sensory loss and concerns *all* elements of sensation. This area of complete recovery of sensation steadily spreads in a distal direction and throughout concerns all the elements of sensation affected by the physiological division, there being nothing comparable to the two-stage recovery after nerve suture. We do not know the precise histological changes consequent upon compression, but, judging from the length of time which commonly elapses in cases of severe compression between the date of the operation of neurolysis and the first stages of recovery, it seems likely that the compressing force frequently has induced a partial, if not complete, degeneration of the fibres distal to the affected point. The gradual spread of recovered sensation from the point nearest the site of operation to that most distal suggests that regeneration follows neurolysis. On the other hand, the fibres are not divided, and there is not in consequence any disturbance of the intraneural pattern during the stage of repair after neurolysis. It seems likely, then, that the absence of the two-stage recovery may bear some relation to the absence of disturbance of the intraneural pattern.

If the explanation of the two-stage recovery submitted in this paper is correct, the relationship is obvious. With the repair following neurolysis in an uncomplicated case of extraneural compression all the old original paths concerned with all the affected elements of sensation

will be re-established, and as soon as they are all complete in their full and original continuity from the periphery to sensory centres in the cerebrum, recovery of full sensation will occur. All the results of disturbance of the intraneural pattern which I have held responsible for the two-stage recovery following nerve suture are absent, and therefore the cruder and the more refined and higher elements of sensation recover together. The characteristic features of the protopathic stage are commonly absent; if present, in my experience, they are only seen over a small part of the affected skin, do not persist for long, and if the skin of the particular region is carefully tested it is invariably found that over this small area the cruder elements of sensation are present and the higher absent. According to the invariable rule, with the recovery of the higher aspects of sensation, the protopathic characteristics disappear. This appearance of even a small area of skin exhibiting the protopathic stage after neurolysis for physiological division of a nerve is quite rare, and this infrequency of its occurrence offers another criticism to the view that the protopathic stage is only a manifestation of incomplete or imperfect repair.

Head and Sherren [6] have found that in their experience after incomplete division of a peripheral nerve sensibility to light touch and to prick are restored together. I have seen this frequently, but not invariably, after incomplete division. Its frequent appearance is, however, in accordance with the statements made with reference to compression, since in partial division there is much less risk of torsion and severe disturbance of the intraneural pattern during regeneration than after complete division.

REFERENCES.

[1] Boeke. "Studien zur Nervenregeneration," No. 2. "Die Regeneration nach Vereinigung ungleichartiger Nervenstucke," etc. (quoted by Stookey). Verhand. der kon Akad. von Wet., Amsterdam, 1917.

[2] Head, H. "Sensation and the Cerebral Cortex," *Brain*, 1918, 57.

[3] *Idem.* "Studies in Neurology." Vol. I, Part i, London, 1920.

[4] Pollok, L. J. "Nerve Overlap as Related to the Relatively Early Return of Pain Sense following Injury to the Peripheral Nerves," *Journ. of Compar. Neurol.*, 1920-21, **32**, 357.

[5] Ranson, S. W. "Unmyelinated Nerve Fibres as Conductors of Protopathic Sensation," *Brain*, 1915, **38**, 381.

[6] Sherren, J. "Injuries of Nerves and their Treatment," London, 1908.

[7] Stopford, J. S. B. "An Anomalous Response to Direct Faradic Stimulation of a Nerve at Exploratory Operations," *Lancet*, 1921, **2**, 73.

[8] *Idem.* "The Nerve Supply of the Interphalangeal and Metacarpo-phalangeal Joints," *Journ. of Anat.*, 1921-22, **56**, 1.

[9] *Idem.* "A New Conception of the Elements of Sensation," *Brain*, 1922, **45**, 385.

[10] *Idem.* "The Anatomy of So-called Deep Sensibility," *Journ. of Anat.*, 1922-3, **57**, 199.

[11] Stookey, B. "Surgical and Mechanical Treatment of Peripheral Nerves," Philadelphia and London, 1922.

FAMILIAL CLAW-FOOT WITH ABSENT TENDON-JERKS: A "FORME FRUSTE" OF THE CHARCOT-MARIE-TOOTH DISEASE.

BY C. P. SYMONDS, M.D., F.R.C.P.,
Assistant Physician for Nervous Diseases, Guy's Hospital,
Assistant Physician, National Hospital, Queen Square,

AND

M. E. SHAW, M.D., M.R.C.P.,
Medical Registrar, Guy's Hospital.

ROUSSY and LEVY [10] have recently reported the occurrence in seven members of one family of acquired bilateral pes cavus, together with total abolition of the tendon-jerks, and in some cases atrophic weakness of the hands. This, they claim, is a clinical picture hitherto undescribed, to be regarded as distinct on the one hand from Friedreich's disease, and on the other hand from the so-called peroneal type of progressive muscular atrophy originally described by Charcot and Marie [3], and by Tooth [15].

The object of the present paper is to record details of a similar family, to compare these with Roussy and Levy's cases, and to adduce evidence for supposing that both families represent "formes frustes" of the Charcot-Marie-Tooth disease.

Case 1.—William C. (fig. 1) is now aged 21. He was originally admitted to hospital under one of us at the age of 16, and has recently been re-examined. During the interval of five years his condition has not altered.

His position in the family tree is indicated in fig. 2. He had measles and chicken-pox as a child, and at the age of 10 an attack of diphtheria. On his own account he was always considered muscularly weak, and as a small child had some difficulty in walking. This was much accentuated after the attack of diphtheria and became progressively worse. At the age of 13 he was brought to hospital on this account, and had minor operations performed on both feet (? tenotomy of tendo Achillis).

He has otherwise led a normal, active and healthy life. For the past three years he has been employed as a motor driver, and is able to take charge of a five-ton motor lorry.

On examination.—General physique is poor, but there are no signs of physical disease apart from the abnormalities to be described in the nervous system.

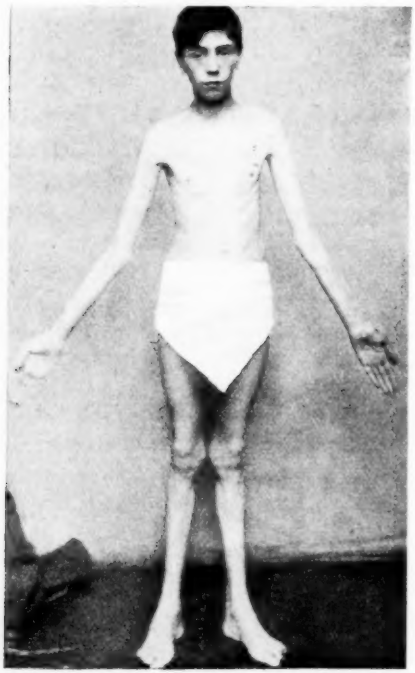
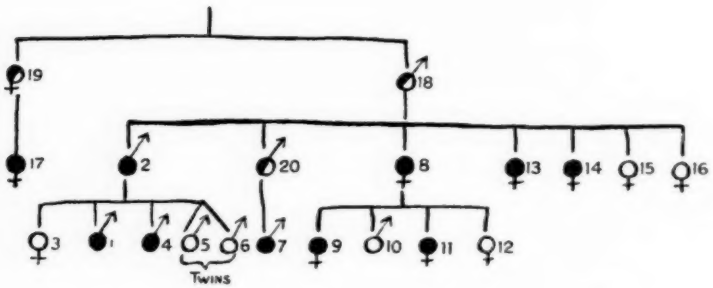


FIG. 1—*Case* 1. William C. at the age of 18.



● = Affected members.

○ = Healthy members.

◐ = Members concerning whom only indirect evidence is available.

FIG. 2—Family tree. The numerals refer to the numbers of the cases as given in the text.

Nervous system: Mental state is normal. There is no speech defect.

Visual acuity is $\frac{6}{9}$ in both eyes, and the fields are normal to rough tests. The optic discs show no abnormality.

Watch is heard at 3 ft. on either side.

His pupils are equal, central, regular and react normally to light and in accommodation.

The ocular movements are full and normal, and there is no nystagmus.

The motor and sensory functions of the fifth nerve are normal.

There is no wasting or loss of power in the facial muscles, and the functions of the remaining cranial nerves are unaffected.

No loss to cotton-wool or pin-prick was discovered, and the senses of position and passive movement are normal. Vibration sense estimated by the quantitative method of Symms is within normal limits.

The muscles of the upper limbs and trunk are of poor volume, but there is no localized wasting, and power throughout is good, better perhaps than might be expected for the size of the muscles. The hands are long and narrow, but there is no wasting or weakness.

The muscular development of the lower limbs again is poor without any localized wasting. The power of individual muscle groups tested separately is good.

Both feet are in the claw position, the toes being hyper-extended at the metatarso-phalangeal and flexed at the interphalangeal joints; the plantar arch is abnormally high and the foot consequently shortened in the antero-posterior line. This deformity is rather more evident on the right, and there is on this side also a slight tendency to equinovarus.

Movements of the toes are freely but feebly performed. At the ankle-joints all movements are good, except plantar flexion which is limited in extent owing to the undue length of the tendo Achillis. The muscles of the calves, anterior tibial groups and peronei, though small, are powerful.

The visual impression of generalized muscular smallness is partly due to lack of subcutaneous fat.

There is no loss of tone.

Reflexes: The triceps, supinator, knee and ankle jerks are absent. The epigastric and abdominal reflexes are present and equal. The left plantar response is flexor, the right was not obtained. There is no loss of sphincter control.

Posture: Normal, the gait rather clumsy but not more so than can be accounted for by the deformity of the feet.

The electrical reactions (examined in 1923) were normal.

The Wassermann reaction in the cerebro-spinal fluid was negative in 1921. The blood taken at the same time gave a positive reaction, but when the test was repeated one week later it was negative. No antisyphilitic remedies had been administered in the meantime.

Case 2.—Alfred C., aged 44, father of Case 1. Examined in 1923. Was quite well until about fourteen years ago when he noticed that his toes began to

"curl up." He attended the out-patient department at Guy's Hospital and was recommended surgical boots. These gave no relief, and he thought no more about it.

He entered the Army in 1914, but the strain of marching drew his attention to the fact that pes cavus was developing, especially in the left foot, and he had to buy his own boots. He left the Army in 1916, but rejoined in 1917. This time he was classed B 1 on account of his feet. His duties again involved marching and he went sick with bad feet. A medical board recommended surgical boots which gave temporary relief.

He is now a bus driver and receiving no pension. He thinks his feet are getting worse, but the right is very slightly affected. He has had no trouble with his hands except a slight tendency for the fingers of the left hand to curl up when the hand is not in use.

He is married and has five children (Cases 1, 3, 4, 5 and 6).

Present condition.—He looks quite fit. Mental condition normal. Optic discs normal. Cranial nerves unaffected except that the right side of the face is slightly weaker than the left. Nystagmoid jerkings are present on looking both to right and left.

Sensation is normal except that the sense of position in the left toes appears slightly impaired. Vibration sense (quantitative method) is within normal limits. The hands are those of a manual worker. The palms are abnormally hollow and the hypothenar eminences slightly wasted, especially in the left hand. Both feet show a severe degree of pes cavus, more marked in the left, and some equinovarus. There is corresponding weakness, mainly in the peronei: dorsiflexion is weaker than normal. Brisk fibrillation was seen for three minutes in the right peronei.

The triceps-jerks present and equal: the supinator-jerks diminished but equal. Right knee-jerk feeble, left doubtful. Both ankle-jerks absent. Plantar reflexes flexor.

Case 3.—Ada S., aged 22, eldest child of Case 2 and sister of Case 1. Examined in 1923. Married, but has no children. Worked in telephone works prior to marriage. She has had no illness except measles as a baby, and has never noticed anything wrong with her hands or feet.

Present condition.—She looks sallow but healthy. She resembles her mother rather than her father in feature and she is quite unlike her brother, William C. (Case 1). She has her mother's brown eyes. Optic discs and cranial nerves are normal. Sensation was not examined. The hands are long and thin, with tapering fingers like her brother's. There is no wasting, weakness or deformity. The feet have high arches but not more than can be accounted for by high-heeled shoes. There is no wasting or weakness. All the tendon reflexes are present and equal. Plantar reflexes flexor in type.

Case 4.—George C., aged 10, brother of Case 1. Examined in 1923. Was quite well until aged 6, when it was noticed that his feet began to turn inwards and he stumbled in walking. There was no complaint of pain. He has had hospital treatment at various times, including bilateral operations for pes cavus (fig. 3).

Present condition.—Healthy-looking child, bright and intelligent. Optic discs and cranial nerves and sensation are normal. Power in hands is good. The feet show scars of the operation mentioned above. There is wasting of all the muscles of the legs, but they were only removed from plaster a fortnight ago after eight or ten weeks. The power in the peronei is fair on both sides.

The triceps-jerks are present and equal. Supinator-jerks diminished on left side, doubtful on right. Knee- and ankle-jerks absent. Plantar reflexes doubtful. Electrical reactions normal.

BIOLOGICAL LABORATORY

FIG. 3.—Feet of Case 4, George C.

FIG. 4.—Feet of Case 7, Gilbert C.

Cases 5 and 6.—Ernest and James C., aged 2½, twin brothers of Case 1. Examined in 1923. Both healthy-looking children with perfectly normal hands and feet. All tension reflexes present and equal.

Case 7.—Gilbert C., aged 10, first cousin of Case 1. Examined in 1923.

For three years past has had trouble with his feet, beginning with pain in

the arch of the left foot (described as "rheumatism"). He had St. Vitus' dance two years ago and was ill for eighteen months, but is now quite well. He is at school and can play games as well as any boy of his age.

Present condition.—He is small for his age and rather sallow, but bright and intelligent. Optic discs and cranial nerves are normal. There are slight nystagmoid jerkings on looking to the left. Sensation is normal.

There is bilateral pes cavus and some equinus without much clawing of the toes (fig. 4). Power in the peronei is good.

There is some flattening of the right hypothenar eminence and both palms are abnormally hollow.

The triceps-jerks are present and equal: supinator-jerks are doubtful. Knee and ankle-jerks are absent and the plantar reflexes flexor.

FIG 5.—Feet of Case 8, Ada B.

Case 8.—Ada B., aged 38, paternal aunt of Case 1. Examined in 1923.

Complains of weakness of both feet. At the age of 11 she had St. Vitus' dance which lasted twelve months. Following this she had pains and occasional swelling of the feet and used to fall about. She was kept away from school from this time onwards as she was not considered strong enough. She took up domestic service when she was 13 years old and married at 24. She has four children (Cases 9, 10, 11 and 12). Of recent years her feet have given her a good deal of trouble and she has had difficulty in getting shoes to fit her.

Present condition.—General health good. Optic discs and cranial nerves are normal: a few nystagmoid jerkings were observed. Sensation is normal in the upper limbs. A few mistakes were made when the sense of position was tested in the toes, more on the left than the right.

Power in the hands is good and there is no wasting.

Bilateral pes cavus is present, with dropped feet and claw toes, the deformity being greater on the left than on the right (fig 5). Power is good except in the peronei; power in the latter muscles is absent on the left, minimal on the right. Dorsiflexion of the ankles is definitely weak.

The triceps-jerks are present and equal: supinator-jerk feeble and equal. Knee-jerks are both weak but brisker on the right than the left. Ankle-jerks are absent.

Case 9.—Gwladys B., aged 14, daughter of Case 8 and first-cousin of Case 1.

She was admitted to Guy's Hospital under one of us in February, 1923, complaining of general wasting. She is said to have had rickets as a baby, and has never been strong. Her mother noticed deformity of the child's feet quite early and recognized the condition as being similar to the one from which she herself and several of her brothers and sisters suffered.

She has attended the Orthopædic Department as an out-patient and has had two minor operations which did not improve the condition. Her mother states that the child has been getting gradually thinner for some time past, but the general health has not suffered.

Present condition.—When examined in hospital she was found to have a marked resemblance, both facial and physical, to her cousin William C. (Case 1). She has the same thin hands with rather long fingers and the same exiguous bodily musculature. She clearly takes after her mother and has all the hereditary attributes of the C. family.

Nothing abnormal was found in heart, lungs or abdomen.

The optic discs and cranial nerves are normal, but there is some nystagmus, especially on looking to the left.

Sensation is normal to cotton-wool, but is recorded as slightly diminished to pin-prick all over the body. Vibration sense is within normal limits.

The arms and hands are thin but show no signs of localized muscular wasting; power is in proportion to the small musculature. There is bilateral pes cavus and some wasting of the leg muscles, especially the peronei, more marked in the right leg. She walks on a wide base and has never been able to run; there is no inco-ordination.

The triceps-jerks are feeble but present and equal. All other tendon reflexes absent. Abdominal reflexes are normal. Plantar reflexes were not obtained.

Electrical reactions: All muscles of the legs respond to the faradic current. The contractions obtained with the galvanic current from the peronei and anterior tibial muscles were rather slower than normal. No change found in the other muscles. All muscles of the arms give normal response to the faradic and galvanic currents. Wassermann reaction is negative.

Case 10.—Frederick B., aged 12, brother of Case 9 and first-cousin of Case 1. Examined in 1923.

He has had no illness except measles and has never noticed anything wrong with his hands and feet. He gets on well at school and plays games.

Present condition.—Healthy-looking child: facially he resembles the C. family, and his mother (Case 8) agrees that he takes after her.

The optic discs and cranial nerves were normal, but fine nystagmoid jerkings were present. Sensation was normal.

The hands and feet were natural in every respect and all the tendon reflexes were present and equal.

Case 11.—Constance B., aged 8, sister of Case 10, first-cousin of Case 1. Examined in 1923.

She has had no illness except measles at age of 3. At age of 6 her feet began to give her trouble just like her sister Gwladys (Case 9). The feet appeared to swell, and she complained of aching and began to fall about.

Present condition.—Healthy-looking, intelligent child who gets on well at school.

The optic discs and cranial nerves were normal. A few fine nystagmoid jerkings were present, especially on looking to the right. Sensation was normal.

Wasting of arms and hands. Pes cavus with claw-toes is present, more marked on left than right. No marked weakness of muscles except on the peronei, which are weaker on the left than right.

The triceps-jerks are present and equal. All other tendon reflexes absent.

Case 12.—Ethel B., aged 6, sister of Case 11, first-cousin of Case 1. Examined in 1923.

Has had no illness except measles, and hands and feet have always been all right.

Present condition.—Healthy-looking child; takes after the C. family.

The optic discs were not examined. The cranial nerves were normal, but fine nystagmoid jerkings were present on looking to the left. Sensation was not examined. Hands were normal except that one of us thought the right hypothenar eminence slightly flatter than the left. The feet are perfectly normal in every respect.

All tendon reflexes present and equal.

Case 13.—Margaret Ch., aged 32, paternal aunt of Case 1. Examined in 1923.

She cannot remember having had any illness except occasional headaches. She has noticed as long as she can remember that the ring and little fingers, especially of the right hand, will not extend properly, but she has never been inconvenienced by weakness of either hand. She has had no trouble with her feet and has never worn high-heeled shoes.

She married at the age of 23, and has two children aged 8 years and 5 weeks. These are said to be perfectly normal (we have not been able to examine them).

Present condition.—Looks healthy. Mentally normal. Optic discs and cranial nerves normal too. Sensation was normal all over to cotton-wool and pin-prick, but she made a few mistakes in sense of position of her toes.

Right hand shows wasting, essentially of the ulnar type; the intrinsic muscles of the thumb are slightly if at all affected. The hand is deeply hollowed and the hypothenar eminence lacking. All the palmar and dorsal interossei are wasted. There is weakness corresponding to the wasting (fig. 6). Left hand is relatively normal.

Both feet show pes cavus with claw-toes, the right more than the left. Power on the whole is good, but dorsiflexion of right foot is slightly impaired. The right peronei exhibit strong fibrillary tremors, causing oscillating movements of the ankle. A similar but feebler tremor, sufficient to produce movement of the ankle, is present on the left.

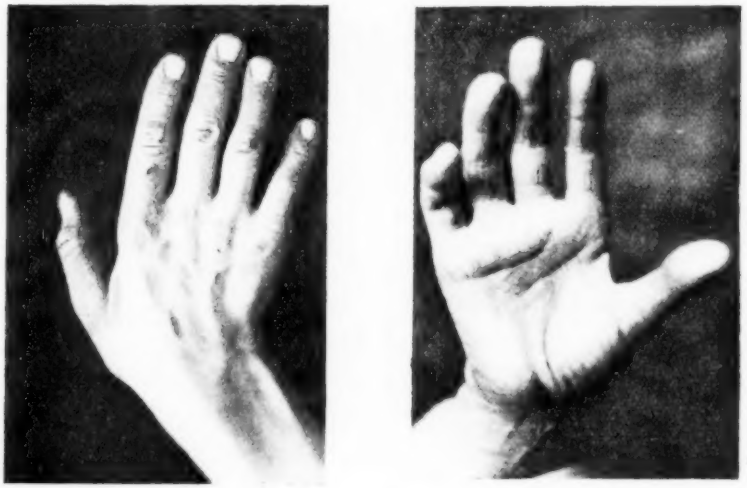


FIG. 6.—Right hand of Case 13, Margaret Ch.

The right triceps-jerk is weaker than the left; the supinator-jerks were both absent. The knee-jerks were equal but obtained in reinforcement only. The ankle-jerks were absent and the plantar reflexes doubtful.

Case 14.—Annie P., aged 32 (when first seen on May 5, 1925), sister of Case 13, paternal aunt of Case 1.

She has not herself noticed anything wrong with her walking and has always worn ordinary boots, but when she was in service at the age of 18 her mistress told her she had "funny feet and funny hands."

She is married and has three children—two boys, aged 6 and 3, and a girl aged 5. She does not think there is anything wrong with their hands or feet.

Present condition.—General appearance is healthy. She is deaf and this

makes her appear rather unintelligent. The optic discs and cranial nerves are normal. Sensation was not examined.

There is no wasting or weakness of the hands, but the left little finger tends to curl up in a position of rest; this applies to a less extent to the ring finger on the same side and to the little finger on the other side. She has bilateral pes cavus.

Supinator and triceps jerks are absent. The knee-jerks are diminished, the left more than the right, and the ankle-jerks absent. Plantar reflexes are doubtful.

Case 15.—Daisy B., aged 25, sister of Case 14, paternal aunt of Case 1. Examined in 1923.

She has had no illness except measles as a child and has never noticed anything wrong with her hands or feet. She is married and has two children, aged 3 years and 9 months, both believed to be perfectly normal.

Present condition.—Facially she does not resemble the other members of the family that we have seen; she is said to take after her mother rather than her father. She is quite healthy in appearance.

The optic discs and cranial nerves are normal. Sensation was not examined.

Her hands appear normal except for doubtful wasting of 4th dorsal interossei, more marked on right. The arches of the feet are both high but not more than can be accounted for by the high-heeled shoes she has always worn. Her toes are normal and there is no wasting in her legs or feet.

All the tendon reflexes are present and equal.

Case 16.—Rose C., sister of Case 15, paternal aunt of Case 1. Examined in 1923. She has had no illness, except measles as a child. Her feet and hands have never given any trouble.

Present condition.—Facially she resembles the C. family and, according to her sister, is like her father. She looks well and strong.

Sensation is unchanged and her feet and hands are normal in every respect.

All tendon reflexes are present and equal.

Case 17.—Mary V., aged 29, first cousin of Case 16, first cousin once removed of Case 1. Examined in 1923.

She has had no illness except measles as a child, and has never noticed anything wrong with feet or hands. She injured the second finger of the right hand at her work some time ago (she works in the printing trade but has nothing to do with lead).

She is unmarried and has one sister and two brothers living whose feet and hands are believed to be normal.

Present condition.—She looks quite healthy. Cranial nerves and sensation are normal.

As long as she can remember her two little fingers have tended to curl up. They are both over-extended at the metacarpo-phalangeal joint and flexed at the interphalangeal joints, a slight claw position resulting. The left hand

shows slight wasting of the thenar and hypothenar eminences, with hollowing of the palm suggesting wasting of the palmar interossei.

Both feet have abnormally high arches and claw-toes with definite wasting of intrinsic muscles. Power is quite good.

All tendon reflexes are absent, except the triceps-jerks which are present and equal but appear diminished.

Case 18.—Alfred C. (senior), grandfather of Case 1—now dead.

The only evidence we have concerning this case is the testimony of his children. It seems clear that he had unusually small feet with high insteps. He was probably affected.

Case 19.—Carrie V., sister of Case 18, great-aunt of Case 1. She is also dead.

According to her daughter (Case 17) her feet were both normal and she wore ordinary boots. Her nephew, Alfred C. (Case 2), thinks she had abnormally small feet. The evidence is inconclusive.

Case 20.—Charles C., paternal uncle of Case 1.

He is still alive, but has not been available for examination. The testimony of the rest of the family makes it probable that he has at any rate bilateral pes cavus. He is said to have small feet and high insteps.

The results of the examination of vibratory sensation have not been included in detail in the above reports. It was examined quantitatively with the Symms's fork in Cases 1, 2, 4, 7, 8, 9, 11, 13 and 17. In all cases it was within normal limits.

Discussion.

A comparison of our description and photographs with those given by Roussy and Levy [10] leaves no doubt in our minds that the clinical picture in the two families is the same, and that the whole series of cases may be discussed as one. We have tabulated the essential features of our group for convenient comparison with theirs (p. 398).

Roussy and Levy [10] in discussing their cases remark that although the association of pes cavus and absent tendon-jerks in their family was at once suggestive of Friedreich's disease, the other features of this malady, in particular the cerebellar symptoms, were uniformly absent. The wasting and weakness of distal muscles, met with both in their family and our own, supplies a further point of distinction, for in Friedreich's disease muscular atrophy does not occur.

As to the distinction from the Charcot-Marie-Tooth disease they are content with the remark :—

"Certains d'entre nos malades pourraient être, en effet, rapprochés de ce dernier type par la maladresse et la faiblesse des mains, par d'exceptionnelles amyotrophies, par des troubles de réactions électriques, et par l'existence du pied bot.

"Mais, à vrai dire, il ne s'agit là que d'une vue de l'esprit, qui, pour séduisante qu'elle soit, ne saurait prendre le pas sur les faits cliniques, ou anatomo-cliniques.

"Sans doute, les vérifications anatomiques nous manquent. Mais en leur absence, et devant un tableau clinique si nettement particulier, nous sommes en droit d'isoler dans un cadre d'attente une forme clinique dont l'individualité nous paraît non douteuse."

Actually the question cannot be so easily dismissed.

MAIN SYMPTOMS OF THE AUTHORS' CASES.

Case	Pes cavus	Tendon reflexes		Localized atrophy	Electrical reactions
1	Present	T : — S : —	K : — A : —	None ..	Normal
2	Present	T : + S : (+)	K : R (+) L (±) A : —	Hands ..	Not done
4	Present	T : + S : R (±) L (+)	K : — A : —	Legs (?) ..	Normal
7	Present	T : + S : ±	K : — A : —	Hands ..	Diminished response to galvanism in left peronei
8	Present	T : + S : (+)	K : (+) A : —	None ..	Not done
9	Present	T : (+) S : —	K : — A : —	Legs ..	Subnormal response to galvanism in peronei and anterior tibials
11	Present	T : + S : —	K : — A : —	None ..	Normal response to faradism; galvanism not attempted
13	Present	T : R (+) L (+) S : —	K : (+) A : —	Right hand..	Not done
14	Present	T : — S : —	K : R (+), L (±) A : —	None ..	Not done
17	Present	T : (+) S : —	K : — A : —	Left hand ..	Not done

In column 3 the following abbreviations were used:—

T = Triceps-jerk.
S = Supinator-jerk.
K = Knee-jerk.
A = Ankle-jerk.

+ = Normal.
(+) = Diminished.
(±) = Doubtful.
— = Absent.

Charcot and Marie's paper [3] was based upon five personal observations and a review of four different families, comprising seventeen cases, from the literature.

The chief characteristics of the disease as presented in their summary are as follows:—

A progressive muscular atrophy beginning in the feet and legs, and affecting hands and forearms only after a lapse of several years.

Relative integrity of the proximal groups of muscles and absolute integrity of trunk, shoulders and face.

Fibrillary twitching in the wasting muscles.

Vasomotor disturbances in the affected segments.

Absence of contracture (pas de rétractions tendineux notables du côté des articulations, dont les muscles sont atrophiés).

Sensation as a rule normal. Cramps frequent. R.D. in the wasting muscles.

Onset usually in infancy, often in several brothers and sisters; sometimes also to be found in forebears.

In the description of the personally observed cases there is no mention of pes cavus, the deformity of the foot when present being described as equinovarus.

The knee-jerks are reported as absent in two of their cases; in two they were present but difficult to obtain, and in the other, one knee-jerk was feeble, the other absent. Commenting upon this point, they remark that the tendon-jerks are observed to be absent even before the muscles upon which they depend have undergone marked atrophy or noticeable diminution in their function.

There is no mention of the ankle-jerks. In the arms the triceps-jerks were present in three cases, absent in one and doubtful in the other.

Tooth's thesis [15], published in the same year, was based upon five personally observed cases. He emphasizes the frequency with which the peroneal muscles are first attacked, hence the title which he proposes of "Peroneal Type of Progressive Muscular Atrophy." He admits, however, that the wasting may commence in the tibialis anticus, extensor longus digitorum or gastrocnemius. His summary in the main accords with that of Charcot and Marie. He remarks that fibrillary twitching is not always present and that degenerative electrical changes may be an early phenomenon. The deformity of the foot is described as equinovarus, and the drawings which illustrate the thesis show this rather than pes cavus.

The knee-jerks in three of his cases were normal, in one absent and in the other variable. There is no mention of ankle-jerks or arm-jerks.

Herringham [7] in 1888 reported a family in which the males only were affected in four generations, the disease being transmitted by healthy females. In the case which is fully described, particulars are given of the feet which make it clear that pes cavus was present at an early stage. The knee-jerks were normal at first, but later diminished.

Sachs [11], reporting the cases of two brothers in 1889, emphasized particularly the onset of the malady with progressive double pes cavus. In these two cases the knee-jerks were normal.

Many cases were subsequently reported, and it is apparent from the literature that any case of progressive muscular wasting and weakness in young persons commencing in the feet, and subsequently affecting the hands, was apt to be included under the heading of the Charcot-Marie-Tooth disease. It seems probable that cases of distal myopathy, familial hypertrophic neuritis and myotonia atrophica were so included.

When post-mortem evidence became available nervous lesions were described by various observers (Sainton [12], Siemerling [13], Dejerine and Armand-Delille [6], Bernhardt [2], Hoffmann [8]). In the main the changes found were degeneration of the posterior columns and atrophy of the anterior horn cells in the cervical and lumbar enlargements, with degeneration also in the peripheral nerves.

In a chronic disease of this kind, however, opportunities for post-mortem examinations are rare, and verification of the diagnosis by this means seldom possible.

Turning to the descriptions of the Charcot-Marie-Tooth disease in modern textbooks of medicine and neurology, we find chief stress laid upon the progressive atrophy of muscles from below upwards causing first deformity of the feet, subsequently the inverted "fat bottle" calf, and, if it involves the lower part of the thigh, the inverted champagne bottle limb. The wasting of the hand muscles is described as beginning at a later stage of the malady and sometimes extending to the distal third of the forearm. The description of the foot deformity varies: some authors refer to foot-drop with inversion, others specify pes cavus or claw-foot.

As to the tendon-jerks, it is stated: "The ankle-jerks are diminished or lost in proportion to the wasting of the calf muscles; in the final arrested stage they are usually lost; the knee-jerk is always retained

and is usually brisk" (Collier [4]). "The ankle-jerks are usually lost at an early period. . . . The knee-jerks remain active, and there is very little tendency for them to disappear, as the vastus internus muscle remains in good condition" (Batten [1]). "The deep reflexes are lost in the atrophied muscles" (Purves Stewart [14]). "Les réflexes tendineux sont abolis lorsque l'atrophie musculaire est prononcée" (Dejerine [5]). "Die Knieppänomene sind in der Regel aufgehoben" (Oppenheim [9]). All the descriptions include reference to occasional sensory disturbance or loss.

As to the electrical reactions, Batten and Purves Stewart speak of quantitative reduction without polar change, Collier of "a tendency to an inverted polar reaction" in the earlier stages.

From this brief summary it appears that the essential clinical feature of the disease is muscular atrophy usually commencing in the feet or legs with a tendency later to affect the hands and forearms.

The order of involvement of muscular groups in the legs is variable. If the intrinsic muscles of the feet are first affected, pes cavus will result; if the peroneal and anterior tibial groups, equinovarus. The wasting is very slowly progressive, and may become arrested at any stage. The state of the tendon-jerks also is variable. Although there is a tendency among modern writers to describe abolition of the tendon-jerks as dependent upon, and therefore proportionate to, the degree of muscular wasting, this is directly opposed to the observations made by Charcot and Marie in their original paper and quoted above, that the tendon-jerks may be lost even when the muscles concerned are neither weak nor wasted. If we accept these criteria, we may conclude that the cases described by Roussy and Levy and ourselves are "formes frustes" of the Charcot-Marie-Tooth disease. The atrophy having commenced in the intrinsic muscles of the feet and having thus caused bilateral pes cavus has become arrested at this stage.

In some members of both families, however, other muscles have been involved. When this occurred, the situation and order of the involvement has been consistent with the diagnosis which we suggest. The abolition of tendon-jerks, which was total in Roussy and Levy's series, has been variable in our own (see table, p. 398); but this again is consistent with the original description of Charcot and Marie.

One of us (C. P. S.) has notes of two members of another family affected by the disease which support this argument, providing a link between the fully developed malady and the "forme fruste."

Case 21.—Mrs. B., aged about 35. As a child she used to turn her toes in, and since then has always had some trouble with her feet. Lately her hands "have been a nuisance"—unless they are quite warm she cannot do much with them.

On examination she is a healthy, well-covered, and sensible woman. Optic discs normal. Pupils are rather small, slightly unequal, and irregular in outline, but react normally to light and in accommodation. Cranial nerves are otherwise normal. Sensation normal to touch and pain. There is no loss of sense of position or passive movement. Vibration sense normal. There is uniform wasting and weakness of the intrinsic muscles of both hands, including the thenar eminences. She suffers a good deal of inconvenience from paralysis of opposition of the right thumb. The other muscles of the upper limbs are normal in size and power. The feet are short, with a high arch and clawing of the toes. On the left there is complete atrophic paralysis of the antero-external group of muscles, except the tibialis anticus, and that is weak. In the right leg there is similar wasting and weakness, but the tibialis anticus is stronger. It shows, however, some fibrillary twitching. The other muscles of the lower limbs are good.

Reflexes: Supinators absent, triceps present but feeble, abdominals present and equal, knee-jerks present but feeble, right weaker than left; ankle-jerks absent.

Case 22.—Her elder sister who came with her had bilateral pes cavus, but no wasting or weakness of the legs or arms. The supinator-jerks, knee-jerks, and ankle-jerks were, however, completely absent.

Of the other brothers and sisters all are said to have broad, short feet with high arches, and the mother, who died at the age of 32 of tuberculosis, is said to have had feet of the same type.

Summary.

(1) Roussy and Levy have recently described as a new disease the familial occurrence of claw-foot associated with absence of the deep reflexes.

(2) A similar family is here described.

(3) A comparison with the cases recorded by Roussy and Levy proves the identity of the disease in the two families.

(4) This disease is distinct from Friedreich's disease.

(5) From a review of the earliest descriptions of the so-called peroneal type of progressive muscular atrophy it appears that the cases under discussion may fairly be considered as a "forme fruste" of that disease.

(6) An instance is recorded from another family of the "forme fruste" and the fully developed disease occurring side by side in two sisters.

REFERENCES.

[1] BATTEN. "System of Medicine," by Allbutt and Rolleston. Macmillan, London, 1910, **7**, 71.
[2] BERNHARDT. *Virch. Arch.*, 1893, **133**, 259.
[3] CHARCOT and MARIE. *Rev. de Méd.*, 1886, **6**, 97.
[4] COLLIER. "A Textbook of the Practice of Medicine," edited by F. W. Price, Oxford, 1922, 1527.
[5] DEJERINE. "Sémiologie des Affections du Système Nerveux," Paris, 1914.
[6] DEJERINE and ARMAND DELILLE. *Rev. Neurol.*, 1903, **9**, 1198.
[7] HERRINGHAM. *Brain*, 1888, **11**, 230.
[8] HOFFMANN. *Arch. f. Psych.*, 1889, **20**, 560.
[9] OPPENHEIM. "Lehrbuch der Nervenkrankenheiten," Berlin, 1923.
[10] ROUSSY and LEVY. *Rev. Neurol.*, 1926, **42**, 427.
[11] SACHS. *Brain*, 1889, **12**, 447.
[12] SAINTON. *Nouv. Icon. de la Salp.*, 1899, **12**, 206.
[13] SIEMERLING. *Arch f. Psych.*, 1899, **31**, 105.
[14] STEWART. "The Diagnosis of Nervous Diseases," London, 1924, 306.
[15] TOOTH. Cambridge Thesis, 1886.

A PSYCHOBIOLOGICAL CONCEPTION OF CONSCIOUSNESS AND ITS DISORDERS IN THE EPILEPTIC.

BY L. PIERCE CLARK, M.D.,
New York.

THE mechanism of consciousness is unknown. We may therefore only theorize regarding the exact psychopathology of its disorder or loss. Before developing the subject on biological lines it will not be out of place to summarize the trend of the present accepted theories of its mechanism. Since the general theory was put forward by Cajal and Duval some thirty years ago there has been but little modification of their views, which are based upon the assumption that the end processes of the neurons in the *mesencephals* have make-and-break contacts at their twig-like projections from their cell bodies; that the nerve impulse may pass over or through the ordinary space separating the gemules at the ends of the neurons, and that the impulse passes from one cell to the other over this intervening space, which is called the synapse. No one has actually witnessed the extension or retraction of these neuron processes, nor has the nerve impulse been shown to actually pass across this intervening space. Yet the theory in lieu of a better one is still extant. Many able physiologists, such as Sherrington, make no mention of consciousness as such and hence have nothing to say regarding its mechanism.

Occasionally a physiologist, like Hill, states that consciousness does not come within the province of physiological investigation. Hill further adds that the ego directing afferent nerve currents through the same strands that formerly vibrated to pure sensations which drew a picture, and hence is the revival of its image, is no more incomprehensible than the liberation of afferent impulses from muscles into efferent nerve channels. That impulses so seldom leave their own paths is more astonishing than that occasionally, when the brain is deranged, an hallucination is caused by the passage of an impulse with far greater force down well-known paths. The rarity of hallucinations may give us cause for wonder. One set of impulses is formed by side-tracking others. In waking states all paths are closed save those which

consciousness is using. The more severe the closure the more vivid is consciousness. On the contrary, in sleep all paths are open and in none is the potential of impulse high enough to evoke consciousness.

Some physiologists, who are more in accord with the biologic views which we shall discuss later, hold that cerebral action need not implicate consciousness at all (Noel Paton). Luciani goes so far as to state that consciousness may not be solely a function of the cortex, and he cites the phenomenon of awareness in decerebrate dogs; he mentions bulbo-spinal and spinal "consciousness" and is generally opposed to a required or static view of the process. Paton further cites the well-known fact that often consciousness is not disturbed in a Jacksonian fit until a certain extent of brain substance is involved. He is also in accord with the general theory, which has a better show of reason, that states of consciousness are mere accompaniments of the physical changes in the neurons by which the resulting action is determined.

Some have gone so far as to suggest that the state of consciousness is largely determined not by the incoming impulses but rather by the effector mechanisms which bring about the action. Paton holds that the seat of fatigue is in this cerebral synapse, and states that after these have failed to act the spinal arcs may still be unaffected and spinal reflexes may be produced. Most physiologists who express an opinion at all are in accord with Starling and Paton, that the synapses are the seats of fatigue on repeated excitation. It may be demonstrated that fatigue appears on the afferent side of the arc and perhaps in the first synapse through which the impulses pass. Starling repudiates the idea that consciousness is due to an aggregation of impulses, but this does not exclude Halliburton's statement that consciousness may be due to impediments to the onward flowing "streams of nervous impulses," and that high resistance brings out a more vivid state of consciousness. He is generally in accord that this resistance to the onward flow of impulses may be the dilemma concept of Dewey and others, although he does not mention it specifically as such. In learning a new art an individual finds the resistance high, but as he masters it resistance is lowered until automatism and habit result. Starling accepts the synaptic theory, in principle at least, and shows how mental work is done though it may not be attended by consciousness, thus contradicting an old and erroneous conception that when acts become habitual the nervous elements are no longer active or engaged in physiological processes.

When we turn to the psychologists' view of the mechanism of consciousness we see a steadily lessening contempt for the biological

views. Many still maintain a decided if not complete aloofness from any data born of biological or zoological experimentation, and seem to hold that there is no relation of sequence of events in the evolution of organisms which can throw any light upon consciousness as exhibited in man. They presume that consciousness is not built up within the organism step by step, but that it is to be considered and understood as a product of the evolution of man as we know him ethnologically and historically. Ofttimes far removed from controllable data, their speculations upon consciousness and its biological derivation are highly absurd. Fortunately their tendency in this direction is on the wane, and such men as MacDougall and Warren are generally receptive to the researches of biochemistry and zoology.

A crude and perhaps unwarranted simplification of the physiological process of the mechanism of consciousness may be briefly stated as follows:—

An impact transmitted from the cord and segmental brain into the telencephalon brings about definite changes in the synaptic relations of the neurons to which the impact is first transmitted. Thence the impact is transmitted to other intercalary neurons—indeed to many series of the latter in the manner already indicated. The transmission of the impact, subject to reinforcement, may continue until motor centres are reached, when an outward or motor expression results. Or the transmission may continue to diffuse variously through the cortex without involving a motor area. Whatever the course of the transmission, it is inevitable that the neurons concerned are involved in sequence. The axon-terminals of the first neuron approach and are approached by the dendrites of the second. The second neuron effects a like synaptic approach with the third, and so on. Just as soon as an impact has been transmitted by a neuron (or has completed its discharge) its axon-terminals and the dendrites of the receiving cell are again retracted, i.e., the synaptic relationship is broken and the neuron is again at rest.

From the foregoing it is perhaps proper to infer that a neuron at rest can have no relationship with consciousness—a resting neuron is unconscious. Consciousness can be present only in active or transmitting neurons—consciousness means cortical transmission. Whatever consciousness is, it is in constant change. We are conscious of a sensation, a perception or thought. A sensation persists as long as the impacts which produce it continue; a perception as long as the object perceived throws its impacts upon the receptors; a thought resolves itself into a train of sequences. Each individual instant of time, how-

ever concerned, immediately enters into the past. Consciousness changes constantly from immediate present to immediate past, and also constantly passes into immediate future. According to Bergson there is no present time for consciousness, for the present moment can be but an instant. When we start to grasp it, it is already in the past.

These elementary facts harmonize with the principles of transmission through the cortical neurons. It is progressive, continuous, constantly receding from the point of entrance of the impact, yet continuously advancing. In addition to mere transmission there is the fact of release of energy, a release in which each neuron successively takes part. The impact is thus continuously reinforced and is widely diffused, but not indifferently in all directions. First it must follow the direction of least resistance, and this must be in the parts most travelled, and where synaptic resistance has been most frequently overcome. It is also probable that the most direct routes to the gateways of exit were originally followed, although as the result of continuous adaptation a process of evolution resulted. In the course of the latter the telencephalon grew, and its neurons became more numerous with augmented faculty of response to enviroment. Numerous association tracts, great and small, gradually made their appearance, so that every part of the cortex became connected with every other part.

This does not mean that an impact which enters the telencephalon is diffused universally throughout the entire cortex. The transmission pursues a limited course, although the neurons may in addition discharge their energy into nearby neurons which do not belong in the particular route of transmission. This lateral transmission is of less dynamic power and tends to die out in the field of primary activity. While consciousness follows the main path it may include to some extent the lateral paths. The field of consciousness may thus be likened to the field of vision. It shades or fades into the subconscious and unconscious.

The train of activity is continuous during the waking period, and may be reinforced, deflected or modified by new impacts. Cessation of this activity means cessation of synaptic transmission, cessation of the amœboid approach of axon-terminals and dendrites. This means unconsciousness and sleep.

The extent of the field of consciousness must depend on the number of neurons called into activity, and this in turn depends on the impacts received, and their number, intensity and character. It is the summation of the activities of all the neurons aroused at a given time which

constitutes the conscious individuality. The latter must therefore be regarded as multiple, made up of groups. Group activity may give rise to the communal consciousness, something distinct from the world at large.

Even in this hurried outline of the physiological and psychological views of the mechanism of consciousness we are more or less consciously aware that such concepts are still too static and preformistic and lack deep insight of the biological soil from which such mental processes have arisen. The final process of awareness of oneself as acting is too important a process to be dismissed so easily. Consciousness is a form of mental activity which has been built up within the organism through and by its activity so profoundly that even in its final shaping of our lives in environmental contacts it has many attributes so significantly primary and simple as to be entirely overlooked unless we make earnest effort to understand some of the main biological sequences by which this function has come into being. We no longer believe that consciousness has a specific anatomical origin even in the cerebral cortex. This latter view is but a relic of the old spiritualistic pathology, as well as the conception that the mesencephalon originated in some manner quite distinct from other parts of the organism. Comparative biological studies have done away with both these conceptions, as well as that of the special faculty of mind, i.e., that there are quite distinct areas of cortical functions or that there are such things as free will, attention, memory, &c., all unrelated and having a specific significance all to themselves. On the other hand we know that consciousness is an attribute of many if not all mental processes; perhaps it is the chief one. One reason why we have arrived at no surer knowledge of its specific qualities is because we have attempted to consider consciousness as an abstraction of the mind, or a split-off process of the body. Many writers on the subject, as we have already shown, still persist in this view. Even mind itself is still considered in a too preformed and rigid a view; it is thought of in terms of structure and not as a living, vital process involving the activity of the whole body. Perhaps it is more reasonable and profitable for us to consider consciousness as a reaction of mind, which attitude would especially appeal to the biologist or naturalist. Whatever view is taken, we must admit that all researches in this field meet under one common law, in the general concept of the unity of living processes of the organism. Many biologists and psychologists start with this assumption, and it is daily winning new adherents. The position is not only safe but is closely allied to colligated scientific fields.

If we maintain that consciousness is based upon the essential integrative development of the organism we may exclude any other scientific source outside the vital structures and responses of the organism. This position is not only scientific, but is a truism in the laws governing all matter in the organic as well as the inorganic world. The phenomenon of consciousness also conforms to this law. The necessity of taking account of the composition of the so-called inherited preformed patterns of structure and function at birth, intricate and ill-understood as they are, as well as the response which such an organism makes to an ever changing environment, has left many loopholes for dismissing and admitting data that befog the main issue of formulating a biological concept of consciousness. The adherents of the older view, the morphologists, have added the static element to the otherwise flexible concept of consciousness, while the dynamic biologists have perhaps over-emphasized the specific significance of the environmental factor. We may here cry a truce to these contentions and endeavour to apportion a fair estimate of importance to the several factors entering into our unitary concept of consciousness as a biological phenomenon that has most intricately grown up within the vital modes of response of the organism.

Consciousness has been variously defined according to the observer's standpoint. We shall not attempt to outline them, but will start with the general truism that consciousness in its earliest differentiation as a distinct process of vital function is an awareness of bodily functions while the latter are in progress. This statement brings the subject within the realm of scientific study just as any other function. As Dewey has said, even our judgments are themselves facts which have consequences, and their value depends upon the significance and quality of these mental activities.

The really unsolved problem of consciousness then is not where it lies within the organism, but rather how this body-mind relationship has been brought about, its mechanism of operation and its mode of activity. We have discussed what is known or assumed regarding the mechanism. We may therefore undertake to make clear how this function of mind has come about. Unfortunately we must start with an uncertainty, for we do not know how the state of awareness originated with the first act, nor all the stages through which the process of integration of the bodily process has passed, as well as the simple colourings of conscious acts, to the final stage of full awareness. Nor is it clear how states of awareness come into full consciousness as seen in our everyday life, in which we are aware of ourselves as acting.

However, with these great gaps plainly indicated we may yet proceed to clarify our subject so far as possible. It is necessary for our progress in this matter to state that there are two fairly distinct schools of belief in regard to the relationship of consciousness and matter, the parallelists and the interactionists. The first assumes that mind and matter are coeval and co-extensive, a colligated system of two processes working together but in no wise essentially interrelated. One might illustrate this by the simile of two separate engines working upon one crank shaft. Interactionism, as the name implies, is that state in which the action of one is immediately dependent upon the other. The vital or functional view is inconsistent with both, for it assumes to show that mind itself is awareness. It would seem that all organisms have some degree of awareness of some or all of their vital functions, but this as yet lacks final proof. We hold that the process of awareness itself is an active process and mind is essentially not structure, but a process. We have already learned that the nervous system is both structure and function, and both of these are at the same time a part as well as a whole of the body. The latter concept is less confusing if we say that all the bodily processes are continually perceived and represented in the nervous system though they may only enter into our state of awareness at certain times. We say they do not enter or occupy our attention for the moment. The causal relationship between mind and matter implies that bodily processes of the physiological type may cause certain brain tissues to react in patterns with the function of consciousness, and conversely. Thus one may simply say that lifting a heavy weight repeatedly gives rise to a consciousness of fatigue, and conversely a state of conscious fatigue may cause one to stop trying to lift the heavy weight. Thus each separate experience in some measure modifies the nerve structures, and subsequent experiences are affected by the totality of these past modifications (Warren). We know the processes which constitute our subjective experience—our awareness—and how it has arisen genetically, but we do not know its physiological problem nor the metabolism related to it. This is again comparable to our knowledge that the union of sodium and chlorine makes common table salt, but of just what the atomic or molecular transformation in the process is we are wholly ignorant.

Consciousness, then, as viewed biologically, must be regarded as a part of a complex vital mode of an elaborate process or processes, and as such must be considered in its causal relationship to such processes. As we have said, consciousness is a causative factor to vital modes of

response, and conversely is caused by complex neural and bodily activity. One might illustrate this by saying that muscular contraction is not the cause of the movement of the arm, but rather that the muscular contraction is *one* of the countless factors in an intricate process which eventuates in a given movement. It is true the two states may be taken out of their full relationships and each studied scientifically, but we then again do violence to the other related facts if we do not constantly bear them in mind. Consciousness psychologically considered has already been abstracted from the other factors of conduct, for its special attributes are subjective and objective awareness, and one of the major divisions of psychology is concerned with reintegrating this state of awareness (consciousness) with the data of anatomical psychology. Consciousness may be rightly thought of as one of the modes of matter in motion. Its larger setting embraced in mind is but one of the general vital functions of the body acting as a whole. All our conscious processes are thus but a part of the general physiology of the body, knit into the vital fabric in just the same way as any other mode of behaviour of living substance.

These views are but the extension of well-proven laws underlying general physiology and biology. All human behaviour gives evidence of conscious processes, and profoundly affects the subsequent course of biological and even inorganic events. Consciousness may be conceived of as having a structural and functional history analogous to respiration and locomotion. As we have already stated, consciousness—the dominant instinct of human control—strikes its roots deeply in a biological soil wherein we can detect no evidence of any psychic factors. It appears to have grown up within the individually modifiable modes of behaviour, and in its highly elaborated forms it is the chief factor in the supremacy of the higher mammals.

We are quite in the dark as to what manner of consciousness first emerged in evolutionary history. The evidence seems to indicate that functions of the physiological type antedate any awareness of the fact that they are in process, and that so long as these mechanisms are running smoothly and satisfying the physiological needs of the organism no consciousness is needed or provided. Modifiable functions in general, and consciousness in particular, seem to arise only when the stereotyped action system fails to eventuate in appropriate (adaptive) behaviour; the latter then engenders maladjustment, stasis, internal resistance, and irradiation or overflow of the nervous currents into unaccustomed or new channels. The nervous mechanisms adequate for such a view are

well known. Stable reflexes follow well-defined nervous pathways closely knit together; they are broad highways worn smooth, as Sherrington expresses it, by sheer process of heavy traffic. But these roads are by no means walled off from surrounding fields. Countless bypaths diverge from them in every direction, and a traffic block may sooner or later be relieved and the traffic diverted to other roads, ultimately to reach the original or perhaps some other destination.

This conception is sound physiologically despite some objections which have been raised by psychologists. The claim to which Kantor [7] takes exception, that "synaptic resistance is the cause or condition of such complex action as remembering or knowing," is not here made, for we do not know the mechanism of conscious processes. It is claimed, however, that we have adequately controlled observations which point to the conclusion that consciousness as a biological function does not arise under conditions of unimpeded neural discharge through the physiologically directed pathways of the ordinary reflexes, but rather that its presence is observed under conditions of impediment to such free-flowing processes.

The correlation centres, where competing or conflicting reflex systems are brought into colligation, are regions of high metabolism (their blood vascular supply is always richer than that of neighbouring regions) and, in fact, they are centres of physiological dominance in the sense already explained. Discriminative reactions of reflex type require more time and a greater expenditure of energy than do simple reflexes, though in the end the actual muscular movement may be identical in the two cases. The higher types of discriminative reaction described psychologically as choice, solving a problem or fabricating a new design, may require still more time and much greater expenditure of energy. That which we call mental work is also physiological work.

It is in situations of this sort—problems of conduct in a word—that our adult rational consciousness seems to come to clearest expression, and affective consciousness seems to have a similar, though not identical, setting. It is not improbable that the first consciousness was born of such parentage. Dewey has taught us that the dilemma is the mother of mind, and we may add that primordial impulse, the urge, is its father. Both are elementary physiological processes with nothing intrinsically psychic about them so far as we now know. "Physiological choices" are made in every discriminative reaction to mixed excitation, and in the nervous system the mechanism of the "choice" appears to be mechanically determined variations in interneuronic resistance. On

the strictly reflex plane problems of conduct are solved, dilemmas are resolved, by the working out of native impulses through such organization as is provided, and the progeny of this travail is an adaptive reaction —a progeny biologically legitimate but with no psychic endowments whatsoever so far as is apparent.

But in mankind, and probably in many other of the higher animals, the organization is such that the behaviour generated in the dilemma-situation is a conscious act. The nobler parents produce a nobler offspring. That is not to say that consciousness generates the act. The cause of the resultant act is the total pre-existing situation which may or may not have conscious components. But the awareness is in the act and is an integral part of it.

While it must be admitted we are still profoundly ignorant of the mechanism of consciousness, the biological evidence seems to speak decisively in favour of the belief that in both phylogenetic and ontogenetic development the conscious powers arose not with intent to perform certain useful acts, but during and in the performance of such acts. This argument presupposes a stage antedating the appearance of anything which can properly be called mental, psychic, or conscious in the organism in the ordinarily accepted meanings of these terms—a system of strictly physiological impulses or internally determined modes of action. These impulses differ in various species and in the same individual at different ages, depending upon the internal organization at the moment of their expression. They are biologically, not psychologically, determined; that is, at the stage under consideration there can be no appeal to "lapsed intelligence" or to any other hypothesis which would derive them from any pre-existing mental process whatsoever. They are integral components of every organic pattern. They differ from the integrating factors of inorganic mechanisms partly in their more complex patterns, but more significantly in their more explicit forward reference; that is, they are adaptive, impelling the organism in directions which on the whole tend to conserve its welfare. They are doubtless an outgrowth from still more primitive inorganic types of internally determined (or regulatory) adjustments, and they in turn provide the indispensable biological foundation upon which the conscious voluntary activity of man has been built up.

The attempts so often made by psychologists to derive these primitive impulses from any kind of conscious experience involves a perversion of the biological evidence. Clearly the matter faces the other way about. These things are in their inception biologically, not

psychologically determined; and a consideration of the psychological aspects of impulses must follow, not precede, their biological analysis. The evidence strongly suggests that the psychological factors are historically subsequent to more primitive biological types of impulse, and arose upon this as a foundation.

The second form of apparatus of the neural reserves is well developed only in the higher vertebrates and pre-eminently in the association centres of the human cerebral cortex. It is fundamentally different from the other. In the first place the reaction patterns are, in their broad outlines certainly and apparently often in detail, laid down in the innate organization. They belong in the class which we have termed stable or stereotyped behaviour, and are with difficulty modified in individual postnatal experience. The associated reserves simply reinforce, prolong or otherwise facilitate the reflex and instinctive behaviour. In the second case the reserve mechanisms are superposed upon the innate apparatus, they mature much later (wholly postnatal in the human infant) and the patterns of their development are largely shaped by individual experience. They are functionally knit in with individually modifiable behaviour.

The reflexes and instinct actions function in terms of racial experience. The association centres, on the other hand, form in the aggregate the great storehouse of personal memories, the residue of individual experience. These reserves are drawn upon, not like those of the first form to reinforce the administrative machinery of mechanically predetermined reactions, but to co-operate in deciding on the basis of personal as well as racial experience what act is appropriate to the situation. This is a distinction of far-reaching importance.

To state the matter in another way, the reserves drawn upon in reflex and instinctive behaviour are wrought into the reacting apparatus in preformed patterns, while the patterns of the cortical reserves are not preformed. It is just the presence of the cortical unformed or mobile reserves which makes constructive thinking possible. These reserves are represented partly in structural arrangements similar to those which are bound up with the reflex apparatus of the lower centres, but here not shackled to any particular neuromotor mechanism. They are also represented in the mnemonic apparatus, the memory functions being basic to all cortical associations.

All these associational paths are not functionally active all the time, for this would result in a convulsive or chaotic explosion of cortical activity, but they are activated in constantly shifting patterns which are

neither innate nor permanent. This gives the physiological mobility requisite for invoking now this system of reserves, now that, as the pulses of associational activity pass from one nodal point to another in the network of intercommunicating cortical channels of conduction. Thus new patterns of activity may constantly arise, in which present excitation factors are interwoven in revivified mnemonic systems, and so we have the apparatus of originality or so-called spontaneity of behaviour, or subjectively, constructive or creative thinking.

All cortical activities are knit in with those of the innate "lower" reflex and instinctive systems, for they can come to expression only through these and during the fixation of cortical automatisms, and so forth; this relationship is maintained and strengthened until finally in adult life the innate and habitual components of the behaviour cannot be disentangled either in the observation of others or in the most critical introspection.

The germs of impulse, then, can be recognized in the most elementary behaviour of living substance and these can be followed in their gradual unfolding throughout the ramifications of the animal kingdom, culminating in one phase in the irresistible drive of blind, unreasoning instinct, when the moth repeatedly sears its wings in the flame, and in another, in the free act of a man who volunteers to sacrifice his life to save another in the full realization of what he is doing and the consequence.

If one were to venture a speculative answer, it might be suggested that the earliest rudiment of consciousness was perhaps an ill-defined affective colouring of the act. The performance is either satisfying or in a vague way inappropriate. Herrick has said that malaise is the nearest approach in our adult consciousness to this primal type of awareness. Even this feeble ray of mind may serve a useful purpose (in the biological sense) by helping to set the direction of otherwise aimless random activity, and by keeping the appropriate behaviour keyed up to a higher standard of efficiency.

Early in psychogenesis, possibly contemporaneous in origin with generalized or primitive (elementary) affective experience, the acts begin to assume meanings; there is awareness of particular activities in particular situations and the discrimination of pain-situations (correlated with seeking reactions). Here intelligence is born and grows apace with the further analysis of the sense excitations in correlation with their characteristic bodily responses, until finally rational thinking comes to dominate the behaviour. It would be gratifying to be able to

fill in this schematic outline and vivify theory with evidence and generalities with particulars, but the task is beyond our present skill.

An extended discussion of the problems of psychogenesis does not lie within the scope of this inquiry. Our purpose in alluding to the question here is merely to illustrate the thesis that mind considered as a conscious process may be articulated with the rest of nature as an integral factor in the biological realm. Its origin and mechanism are shrouded in mystery, but no more so than are those of many other distinctive vital processes, and the biologist feels that he has made real progress when he has arranged these processes and their correlated structures in a graded series, and marshalled evidence indicating that the members of this series are genetically related.

The mental components of the functional complexes of adult life—the elemental impulsions deeply rooted in primal instincts, the joy of living, the gratification of the desires, the rational analysis of situations, memories, hopes, ideals, the will to achieve, &c.—are real biological causes of subsequent behaviour, including subsequent joys, sorrows, desires, &c. The mental development is no more lawless than is the physical, for the whole process of development is unitary. There is under normal conditions the same freedom to grow, to expand and to fructify in the mental field as in the related physiological field, and there are quite similar congenital and environmental limitations of this freedom. Lillie [8] calls attention to the fact that " the qualities of the best life are thus capable of survival, increase and eventual dominance, equally with those of inferior life—probably more so, since all persistent life requires the maintenance of equilibria, and equilibria are more stable when disharmonies, destructive elements and other incompatibles are absent."

Mental processes blocked by disharmonies or failure to adjust are regulatory phenomena in the ordinary biological sense.

(1) Every event in nature has a past and a future reference.

(2) Every vital reaction leaves its structural modifications which affect subsequent behaviour. This is a future reference of the reactions for it as a determining cause of later reaction patterns.

The past history of a species sets limits within which its further evolutionary advance can be effective, or at least the direction it will take.

Impulse is the driving force for reflexes and instincts and also for all the higher forms of behaviour, the trial and error and exploring reactions, inventiveness, intelligence and all other individually modifiable behaviour.

Out of the biological impulse of self-preservation has grown the consciously directed impulse of self-realization. This comes to be the dominating integrating centre of the individual. The awareness of the self as an individual permits the development of the impulse of self-realization into a purposely directed programme of self-development, the cultivation of ideals and the fabrication of abstract ideas in general.

Consciousness is a higher form of biological regulation, enlarging the control of environment by the organism and thereby both enlarging and reinforcing the individuality itself. Consciousness of the self as acting gives a new impulse to this progressive movement. Consciously directed impulse becomes purpose, and the forecast of future eventualities here implicit is a true cause of present action.

Society did not begin with mankind. Inquiry has often been made into its biological origins, though seldom by students equipped with biological training adequate for the task. In a recent excursion into this field, Child [2] has drawn some instructive comparisons between the apparatus of physiological correlation, integration and control on the organismal plane and the social organization. He states, "The organism is a dynamic order pattern or integration among living systems or units. Social integration is exactly the same thing. He then proceeds to elaborate the thesis that the mechanisms of dominance and subordination of parts in the living body can be followed through the series of compound and colonial organisms to animal societies of separate individuals and finally to human communities. The foundations of social fabric are, therefore, to be sought in the relations of the individual to his environment and in particular to his living environment.

With evolution of the nervous system and its behaviour mechanisms, the fundamentally psychic character of integration among individual organisms becomes always more distinct (Child). In these higher types of integration the dominance is essentially psychic, but the manifestation of this dominance is as truly the excitation of protoplasm of the nervous system as in lower forms of physiological dominance within the body of a single individual, and the socially dominant idea is effective only as it alters protoplasm and determines its behaviour. In this view it is evident that the idea is regarded as a function of the living body and as a cause of other functions, not only in the body manifesting it, but also in the bodies of other men to whom it has been communicated by language or otherwise. Child's argument, the details of which we cannot here follow, is summed up in these words: "It appears that

leadership, dominance, the pacemaker, play essentially the same rôle in social as in physiological integration. Moreover, if the conclusions advanced are correct, there is a physiological continuity, not simply from the physiological gradient to the fully developed organism, but to the dominance of the idea in intelligent social integration."

The earliest consciousness probably arose within the act, not in order to perform the act. So our social, moral and ethical standards have been formulated largely *ex post facto*.

Altruism as well as the egoistic individualism and the higher functions in general, like all other vital functions, have capacities for growth and development. They will expand and propagate if free from external restraint. And, since in the broad view they do or do not promote social health and progress and through these individual welfare, they have " survival value " as this term is used in general biology.

The main plea which I wish to emphasize here is that consciousness in both its personal and its social manifestations is not something developed apart from the organic process, nor even above it; but it has been developed *within* this process. It is an evolutionary factor biologically comparable with all other adaptive functions. The simple physiological, the instinctive, and the intelligent types of behaviour are all present in the life of every higher animal. All impulses have both a retrospective and a prospective reference. As members of a causal sequence they represent results of previous living and in turn they cause the next following behaviour. Impulses commonly classed as of the biological type (tropism, reflex, instinct) have a blind—that is unconscious—prospective reference in that they are adaptive, meaning that they are so organized as typically to benefit the organism or the community to which it belongs, and this adaptation when viewed retrospectively is seen to have been brought about by biological agencies such as natural selection.

Disordered Consciousness in the Epileptic State.

If we are to evaluate properly the loss of consciousness in the seizure episodes of the epileptic state, it is necessary for us to orient such phenomena and note what relationships these more intense epileptic symptoms bear to the epoch out of which they naturally develop. I have shown elsewhere what the main defects of the primary endowment of the potential epileptic are, and how these impulsive tendencies are so greatly aggregated about the ego as the pivotal point in character evolution; and how the formation of such modal types of organismic-

environmental response are fashioned in such kinds of habits which narrow the life range of interest and harmony. I have shown how the whole evolution of the individual is warped and distorted in a disequilibrated pattern of make-up. Then upon these disordered personal attributes is thrown undue physical and mental stress and the epileptic seizure epoch is inaugurated. If we look upon consciousness, therefore, to be a vital mode of organismic response, anything that distorts the latter from within or without will naturally vary this modal pattern. Therefore, when we say that an epileptic loses consciousness we really mean that there is a disruption of the harmony in the mind processes as as a whole, which in turn controls the modal responses of the entire organism. We might properly say that the whole vital response or habit control of the organism is disrupted. The degree, the depth of disintegration and the successive order of disturbance in the subordinate reflex systems are indices of the amount or severity of the seizure. Everything else being equal, it is possible for us to estimate the severity of the attack by the degree or depth of disintegration of the vital response during the length of time this state endures. The latter is really an index to the resiliency or recoverability of the vital responses which have been disrupted, as well as the amount of damage which the organism has received. If we were permitted to think the dominance of the mind over the organismic control is in the orderly manner by which we customarily think it has integrated itself throughout the reflex systems segment by segment, it would then be possible for us to state accurately just how deeply the whole organism has suffered disorder; but we have already learned that the higher or more lately elaborated mechanisms of neural control are so arranged that every part of the body is in close communication with every other part at one and the same time; hence we cannot say that a particular seizure resulted in a disorganization down to the spinal level, but rather we should say that certain types of vital responses are lost in a functional sense as subtending the whole individual rather than purely anatomically in this or that system.

Too much time has already been spent in attempting to define the significance of certain types of loss of consciousness by neural systems anatomically considered, or even by physiological processes. In other words, the loss of vital responses in the organism at the onset of seizures is of the individual or organismic type; for instance, the epileptic stands still, assumes a rigid or set pose, or he does a series of quite unusual acts which are out of place in the life setting in which the attack occurs. If on the other hand we spoke of the epileptic

individual as losing consciousness of specific and vital modes of response in somewhat the same order as he acquired them, we would more nearly come to an understanding of the significance of the variable disorders in consciousness which accompany the specific release phenomena which the actual attack is. In other words, even in their involutional disintegration the vital modes of organismic response carry with them in the seizures a corresponding alteration in the organismic-environment awareness. These organismic processes may be dimmed or only temporarily benumbed in disorganization, and so the disturbance in consciousness may be only temporarily disorganized. Had we a precise means of accurately measuring the degree and depth of disturbance in the vital modes of response and their recovery after a seizure, we should be able to posit the exact disorder which consciousness suffers. Though the epileptic may seemingly recover quickly after an attack one finds by even our present means of detecting normal responses that full recovery is often delayed for hours or days. This is equally true of the function of consciousness as well as simpler tests of reflexes, physical acts or habits. This tends to show that the organismal processes, from the highest functions in consciousness to the most delicate environmental or social contacts, are all closely integrated in the whole life process. It will ultimately be reckoned as absurd that we may not tell when seizures are to occur, just as we have learned to predict the occurrence of storms and earthquakes.

We may rightly assume that anything which interferes with the epileptic's behaviouristic pattern or habits may tend to disorganize and deteriorate the epileptic individual. The nicety of healthfully maintaining the delicate balance in such individuals is our main therapeutic aim. Just what does stress entail upon the mind process? It has a tendency, first, to increase the habit pattern of response. We say the epileptic individual is harried, harassed, overpaced, bewildered, &c.; the function of mind and consciousness of it is overtaxed, and awareness is forced to a higher level. Inasmuch as this cannot be healthfully maintained there soon results a maladjustment of the whole organism, a stasis occurs and internal resistance is engendered. If the stress is not relieved irradiation or overflow occurs, and new and unaccustomed channels are used which are still within the realm of natural acts. If these are not adequately provided for, the urge of the desire (organismal will) turns back upon itself, "back-fires" or "blows out the fuse," if one may be permitted to use these terms, and an epileptic explosion is soon in progress which results in a discordant disruption of vital modes

of response (habits), and consciousness which is related to these modes is lost, and that, too, very early; for it must be remembered that in the evolutional order of its development the higher processes in awareness (consciousness) are the later acquired functions, especially in the nicer adjustments of organismic adaptations in the life process.

We are aware—in the majority of cases at least—that the seizure epoch in epileptics does not develop by a slow gradation of slight losses to intense and prolonged loss of consciousness, and this prevents our considering the disease phenomena, as one might like to, as an experiment, noting the process of the loss of consciousness step by step. The first attack may be *grand mal*, and only after considerable time, and especially under sedatives, may the discharge convulsion be so slowed and rendered incomplete that we may note the orderly process of the very beginnings of the break in consciousness. The question is pertinent, Why do we not have slight disorders of consciousness rather than actual short or brief losses, finally ending in prolonged losses? In other words, Does not the occurrence of a typical *grand mal* at the very outset of the seizure-epoch disqualify our concept of the mechanism of the disorder of consciousness in epileptics? In answer it may be said that in the neural mechanism there is the all-or-none theory, which has been fully expounded in other works. This hypothesis may be invoked; like the explosion of gunpowder it is either exploded or it is not, and *all* the charge is fired off or none. Carrying the analogy a little further, the amount of explosion in any given charge may be likened to the breadth of irradiation of the discharge throughout the associated centres. The co-ordination centres, the neural mechanisms through which the discharge convulsion undoubtedly acts, embrace an enormous conflicting system of reflex processes opposed as well as colligated. All these centres are those of highest metabolic instability. The back-firing in the attacks calls forth the indiscriminate employment of many conflicting types of discharge, so that the muscular convulsions alone may take on the appearance of a "clotted mass of movement," accompanying which disorderly processes of mind likewise participate in the greatest disharmony. Consequently we have a true and profound loss of consciousness paralleling the severity of neuromuscular discharge, so there may be presented in the seizure-epoch of the epileptic all sorts of disturbances of consciousness which are usually proportionate to the intensity and spread of the irradiation discharge in conflicting and colligated cortical systems. Just as the discriminate reactions of high reflex types require more time and energy for their integration and performance, as well as

the psychological choice solving problems or fabricating new designs and the like, their high instability in the involution of the attack may be discharged so rapidly we may not note their several functions. The temporary exhaustion in mind and body are indications of the amount and kind of discharge. Viewed from the seizure episode, the epileptic process and the whole sequence of the stages of deterioration are epitomized in the rapid, condensed epoch of the attack; it is an acute disorganization or disruption of the normal modal pattern reaction (habits) of the whole epileptic individual. If not relieved it leads to a deterioration of the whole individual in mind and body. Just as habit disorganization fails, the memory and mind process fail, as they are but different phases of one and the same process. In condensed epileptic moments we have seizures and loss of consciousness, and in the prolonged disruptive processes we have a more or less permanent deterioration. Just as we noted that one of the main functions of consciousness was to carry the organism forward to an adaptive end, its disorganization or loss slows up this process, or it ceases altogether and a retrograde movement towards deterioration begins. If the life process cannot be made to overcome these organismal faults the individual is doomed: more frequent and severe losses of consciousness occur until the mind process is blotted out in dementia. We then have left the prenatal brain mechanism of the first or instinctive order which probably carries the habits, instincts and impulses of the family stock or racial inheritance. One might rather statically place the matter thus: the memory seemingly fails at the early advent of seizures, and that, too, in the mildest types of rapidly recurrent *petit mal* or in the loss of consciousness solely. This may be regarded as at the biologically interrelation point of the reserve with the instinctive system, the stress of disorganization may be placed upon this pivotal point, which is the basic foundation of the whole reserve or experiential system. The flexible or modifiable behaviour rests upon this mnemonic system. The purely static concept here is somewhat relieved in that all spontaneity of behaviour as well as creative thinking are closely interwoven with daily revival of mnemonic system. Moreover, one must not think of these two systems in the adult as having a possible separate functioning; only chronologically are they separate in biologic organisms. We may say that the interruptions in consciousness, which are the chief distinction of the seizure epoch, are an *index* to the degree of defect with which the organism fails in an orderly progress in the life process. Its clinical importance need not be minimized, but the indicator should not usurp

the engineer's concern in the whole working process of his apparatus. Nor should he fail to note the more obscure but important mechanisms of the organism which lie behind the indicator and which are of more dire portent. Looked at purely as an indicator of the most delicate adaptations of the organism, the loss of consciousness may give us a real insight into the defect of the life process of the epileptic.

We have defined, in general terms the nature and vital significance of consciousness as an organismal process. In the epileptic we are signally debarred from directly applying such knowledge save in very general terms, for we do not know the mechanism of consciousness nor the physiological processes that subtend it. As regards the mechanism, to say the fault lies at the synapse does not help us much, for we need to know why it should appear here and not elsewhere in the organism. We do know that the severity and degree of loss of consciousness indicate the degree of general disintegration the individual epileptic suffers. Usually it is first shown by the slightest absences, and gradually passes into the severer *grand mal* attacks. These phenomena of disturbance in consciousness are but indications of defects in the organismal mechanisms, and the gradual disintegration of the cortical dominance for further control over these progressive patterns for adaptive living. The associated reserve of pattern and function is thus probably the one most injured in epileptics. The type of idea dominance in the personality make-up cannot find a tranquil lodgment in the altruistic world and an intropsychic conflict is set up, so that the epileptic personality is thwarted and recoils upon itself with ever increasing intra-organismal tensions of one sort or another until the organism breaks under the strain in loss of consciousness, and finally, if not adjusted, in mental deterioration. The consciousness of the epileptic is slowly built up out of the integrations of his impulsive instincts, as shown in his bodily and mental processes, dominated by the central impulse of his personality, the egoistic drive or urge; he may then be said to have an egoistic consciousness as contrasted with altruistic dominance.

Strictly speaking, these types are never pure; it is meant only to convey the preponderance of a personality rather than a totality of make-up in either. Given, therefore, a type of make-up that is handicapped by inheritance, adaptation is undertaken with great difficulty. Social adaptations are onerous to the epileptic; the process is attended by increasing strain until the break in adaptation occurs. Inasmuch as his repertoire of pattern of reflex and instinctive life has distinct limitations and is of its very nature rigid and tends easily to become fixed, every

intense effort to co-operate has a tendency to heighten the whole state of awareness. If he were able to endure these disharmonies and life dilemmas he would undoubtedly become the superman which his impulsive egoistic nature strives to impose, but he is in hopeless conflict with his innate inferiority which refuses to lend itself to such herculean tasks, and a seizure or back-firing of his forward progression of adaptation ensues. We have already seen how varied are his inadaptive patterns of behaviour and they are as numerous as his inventive emotional life affords. We may not say that the loss of consciousness really does anything to the epileptic : it is but an index to the stress to which the mental processes are put in adaptation. Again, the whole mental process in its abolition of activity really does nothing to the epileptic, but rather these processes are conscious group indicators, mental syndromes, of the organismal stress of maladaptation all the way down or up through its different levels of integration, from the most primitive metabolic to the highest idealistic process.

If one wished to urge a field of physico-anatomic research, the colligation and association processes of the cortex in epileptics would, perhaps, be the region in which one would find some answer to the fixed and rigid patterns of the epileptic make-up. Though even here one might find a defect of the trial balance of the epileptic organism, and not its signal defects, in the basic integration of all the bodily processes of which the cortex is but the representative sum-total. Knowing as we do that the reflex and instinctive patterns are prepared from racial inheritance, and the correlating and associative mechanisms are first requisitioned after birth and carry the individual training and experience, we see the prime importance of earliest training in the epileptic child so that these two great life processes may be colligated as much as possible. The point of greatest conflict lies between these two systems or natures. It is an intra-organismal conflict in the effort to find a proper adaptation at the psycho-social level.

Other and lower adaptations in the organism are at fault too, but they are but side issues, as it were, to the main principles in the life conflict. One of the main defects in the mental processes of the epileptic is manifested in the loss of memory. The actual loss of memory is not so extensive as it seems to the epileptic, but that it exists to some degree is a striking and early symptom, present even in epileptics with few attacks and quite independent of the frequency or severity of the seizures. We know that all the associated processes of mind are built up out of the mnemonic systems, and if conflict engenders

stress upon the conscious process of adaptation, disorganizing the adaptive mechanisms of the cortex, almost at once the memory reserves may be injured, thus lowering the psychic conflict. Therefore the memory loss is indirectly a protective mechanism from a too ambitious struggle to adapt to the environment.

When we try to apply more definitely the general principles of consciousness that we have laid down here to the clinical aspects of the disorder of consciousness in epileptics, we pass from fairly sure ground to a field not so fully proven by documented evidence. If we consider consciousness as an affected awareness of the adaptation of the organism to the life process, the essential aim would be to keep the organism directed toward a better appercepted and adjusted environment, a state of equilibration in a changing life process; anything, therefore, that interferes with such a process would be shown in the function of consciousness. We may suppose that in the normal state of consciousness where the organism is not unduly taxed, the inner and outer relationships are adapting and making toward a healthful state; the individual is then keen and alert, or has a tranquil and natural mental grasp of himself and his environment. Anything that lowers the organismal desire or distorts the appeal in an environment necessarily diminishes the vividness of the consciousness.

We have learned that as a rule the epileptic objectivates himself poorly unless he can carry a part of his egoistic interest into specific tasks or purposes. At a relatively early period when his powers of adaptation are less rigid he makes some feeble attempts to objectivate his love interest, but this striving soon fails and it returns with all its passion to his idealized self (narcism), and there remains fixed for the most part, building larger and larger at the expense of a tranquil and sustained effort to adapt to his environment. It is not difficult, then, for us to comprehend that the epileptic apprehends his environment poorly, not merely in intellectual fields, but more particularly in the proper objectivation of his emotions. The narcistic concern of the epileptic limits the wide range of the affective life, and his supersensitiveness limits the depths of his emotional feeling toward the environment. The field of consciousness is insecure and lacks variety and richness. This defect is innate and a real part of the epileptic character. In consequence one finds the field of consciousness disturbed by fantasies, transitory deliria and befogged states. Whenever various stresses are experienced, especially social ones, the epileptic takes but a feeble grasp of his external world, and the functional protection is

evidenced in twilight states, &c., but, of more importance, there succeeds a narrowing of the field of objectivity. This holds true for many another psychotic situation, notably in the shrinking in consciousness in shell-shocked soldiers [1]. With the retraction of the field of object-consciousness there succeeds a heightening of subject-consciousness or self-awareness. Indeed, the two are but parts of one and the same process. From the very nature of the fit one would expect this to be so, i.e., if the breadth of the field of consciousness is normal that part which remains would be more intense.

In grand seizures, where exact data may not be obtained due to the suddenness or severity of the attack, we judge by the epileptic's appearance and manner that he is in a state not dissimilar to that experienced by epileptics who are able to describe their feelings in the twilight state which accompanies milder attacks. In the severe types of attacks we find the epileptic has narrowed the awareness of his environment to the most intensive egoistic concern. Indeed, the mental content in all the automatic states confirms this view, as has been shown elsewhere. The epileptic answers in disjointed sentences in the optative mood as: "I am trying—," "I want to," "I'd like to—," "I wonder—," "I thought—," and the like.

It is therefore quite understandable why self-awareness should be increased in the milder attacks because of the narrowing of the field of normal consciousness. As the state of self-awareness, as we have been considering it, disappears in *grand mal*, there is an inflation or disturbance of the real unconscious, motivated by such an egoistic drive that it is manifested in acts of violence in the automatism, or is engrossed in a most intensive egoistic concern, as shown in fragments of thoughts or states of lethargic *Allmacht*. The condition is then one of complete power over the state of being after an entire abolition of all phases of reality.

The state of epileptic reaction then is an involution of the normal development of consciousness. The latter is gradually evolved out of the self-awareness to that of a wide and rich combination of both subject and object consciousness, or a unified composition of both. If we assume the foregoing to be generally true, and that the epileptic reaction is an involution of the slowly built up normal consciousness of everyday life, one may understand the enormous psychic importance of the fit. First, it has a definite deteriorating influence upon the power of sustained interest and attention, and the tranquil orderliness of the normal objective mental life. As a result of this involution previous memories and sustained attention fail, even though only mild seizures

occur. In this assumption we can understand the often indifferent attitude which the epileptic assumes relative to recovering from his disorder, as each attack refreshes and satisfies his cruder self-awareness and enriches his egoistic interests. To ask him to forgo this unconscious self-gratification and give up his morbid purpose, often falls on deaf ears. Our continued appeal must therefore be along lines of intensifying his personal satisfactions in everyday life comparable to that which he derives from his epileptic habit. Nothing less will avail. It also makes clear that possessing such a relatively simple and crude pattern of personality, the epileptic is loath to accept a life of self-denial and to give up his egoistic concerns which yield him so rich but so destructive a return.

On specific investigation into the slighter grades of *petit mal*, we find that one patient makes the statement: "When a *petit mal* occurs, I can usually control myself and go on talking or continue what I am doing, and the *petit mal* is not apparent to others; there is a sort of turmoil in my mind. This lasts only a second, and afterwards I feel the same as I did before." Another patient says: "I feel intently aware of myself, and a feeling of wonder comes over me: I think, 'Why am I here? Why is the world, anyway? How did I ever get here?' This feeling lasts but a few seconds. It never occurs when I am actively engaged in work in which I am genuinely interested, but comes on between times when I am doing nothing." A third patient states: "During the confused spell I have a feeling that I must not let anyone know there is anything unusual, and that I must retain my poise at all costs. These spells are liable to come on at any time, no matter whether I am busy or not. During them I am thinking of what I intend to do, or of something I should like to accomplish. It may be some problem that comes up during the day, or it may be some task immediately at hand at the time the spell comes on. I feel a desire to keep myself intact. Consciousness, so far as outside affairs is concerned, is suspended, and my attention is directly turned in upon myself." A fourth patient states: "Following several light spells, or even as a spell comes on, I feel that I must not let anyone see what is going to happen. I am aware of all that is going on about me, but cannot take part nor have I any desire to do so. I am inclined to think that there is more or less of a disagreeable feeling about these light spells, but I cannot state definitely just what this disagreeable part is. At other times I feel that no matter what happens I know it is going to be that way, and that if a person speaks I know just what is going to be said. In fact, I feel I have the ability to foretell events and otherwise regard myself as

a superior being at such times. On the other hand, there is another feeling that follows mild disturbances, and that is one of being wrong about everything; no matter what I do or what is being said or done about me, I have a feeling that I am in the wrong. This feeling has come up only recently and follows a series of mild disturbances." Still another patient states: "I could always control these attacks if I really wanted to, but I let them come up. I let them come and then I feel better. Afterwards I feel quiet, soothed and free from tension. They are a deep-rooted satisfaction to my soul."

An epileptic boy, suffering from a continued and enduring epilepsy, gave a description of his *petit mal* attacks as follows: [4] "As the absent-minded spells come on, I dream of something far off—the ideas are all mixed, just like a dream when I am asleep, or when I am at a party and lots of boys are around, or when we are playing Indians. Usually I am flying in the air, or something. I am having a smooth sailing about. It is never unpleasant, but just fine. The harder and longer the dreamy turns are, the more satisfied I seem to be. I wander, float away; maybe I glance against something and then shy off again to float about in a different direction. I only remember the beginning and the ending of the hard ones (*grand mal*), but in the moderate-sized ones I get the most definite dreams. I take up the things around me and make the most fantastic and queer things out of them; I think people moving about me are really trees, and their talking is running water and wind blowing about. As I gradually go into the deepest part of the severe attack the dream grows more confused and mixed up; it gradually fades out, and I simply lie in the air. I float without moving, and my feelings are as though I don't care about anything; it is so peaceful and quiet, and I am very happy. I feel as though I want to keep on going, as though I didn't even have to breathe. It seems as if the attacks come over me and enfold me like great floating blankets."

It seems hardly necessary to comment upon the self-anamnesis in the attacks as being a beautiful, almost allegorical, decription of a return to infantile instincts and desires.

Another instance is a young woman whose *grand mal* epilepsy has been in evidence since puberty [5]. She volunteered the information that the minor attacks were most desirable, and were encouraged when she was alone, and particularly when in bed. She then felt that they were pleasurable, quieting and soothing, as though going to sleep; she pulled the bedclothes over her head to enjoy them to the utmost, and if anyone came into the room, shook her, or distracted her attention, she

felt irritable and said, "Can't you leave me alone? I wish you would not bother me." A further description of vaguely remembered things that happen to her when actually in a sensation is almost identical with the boy's account just given. In sensations of moderate severity, she invariably says: "Yes, yes, I am quite all right; why, certainly,"—there being a manifest desire to fend off anyone attempting to do anything for her that might tend to abort the sensation.

Another epileptic [6], a man in the thirties, experienced an unpleasant sleepy feeling after dinner. At such times he would allow himself to "drift off" into a reverie. He then feels as if he goes off into space, as if he were still only vaguely conscious of something about him and knows where he is and what he is doing. This detachedness from reality and the states of lethargy are but heightened states of subjectivity in which the inner life dramatizes itself, somewhat like day dreams and the states of mental abstractions which are common enough in those not epileptic; but that which gives them a distinct pathological import is their unmanageableness—the slipping away at times from conscious control at the behest of something in him "that demands" appeasements—in other words, the unconscious demand makes itself felt, and he has an epileptic reactive setting of an otherwise common enough everyday abstraction (minor automatism). He often experienced a sense as though people were about as in a dream. The scene and visualized sensations were of the character "as though he were in the centre of it all, and all things centred about him." The general physical sensations were always unpleasant and distressing when translated into conscious terms, or when he was fully free from them. Yet while being experienced they were all pleasant and harmonious.

Another male patient, just before the sensations are to occur, often feels a lack of rapport with those whom he may be with, and a sense of indifference or boredom follows, in which he feels a heightened sense of his own body and mind, and a "detachment from others about him" (increased subjectivity).

We freely admit that the mental content is not always pleasurable in its manifest content, although many of the citations here bear that significance, but that its ultimate or deeper significance supplies as egoistic a satisfaction as the essential analysis of dreams has proven.

Finally, we must state that scientifically there is no loss of consciousness, as such, in the epileptic fit. There is but a retraction of the field of consciousness and a corresponding heightening or intensification of subject-awareness, and this latter state in the severest attacks may be narrowed to the deepest infantile concern of egoistic life. It

would be nearer the truth if we spoke of the state as a disorder of consciousness rather than an actual loss.

We may summarize the foregoing by stating that consciousness is but one of the important accompaniments of the mental processes, and that it is a most delicate index of the free working of the neural processes which are colligated in the field of awareness at any one instant, and that the disorder of this function of consciousness indicates that the highest neural processes, the mental and bodily habits, are not properly integrating the living activity of the organism to an adaptive purpose. The loss or disorder of consciousness then being so intimately bound up with the other mental and neural processes which are in process of disorganization, we must look to the whole vital responses of the organism to make clear just what is transpiring in the epileptic reaction known as the fit. To perform this task properly we must turn to a discussion of the convulsive aspects of the seizure epoch. Consciousness and its disorder in the fit, as we might already suspect, is so intimately bound up with the disordered act or acts that the two must be inevitably associated.

We must admit that our deficiency of knowledge of the mechanism of consciousness and its metabolic physiology hold a specific and relentless grip upon our knowing exactly what happens to the individual in experiencing a fit, but this gap in the chain of events does not hinder our knowing what happens to the organism before and after such phenomena. By taking a strict account of the general efficiency of the epileptic organism in the life process, we steadily gain a clearer knowledge of that process and the series of vital reactions concerned in the defect. Habit disorganization and deterioration are our main concern here, as elsewhere in psychopathology. Just why the epileptic, of all nervous invalids, should show a specific reaction of a loss of consciousness and a convulsion as his particular manner of deterioration is our chief study.

REFERENCES.

[1] Bird, C. "From Home to the Charge; a Psychological Study of the Soldier," *Amer. Journ. of Psychol.*, 1917.

[2] Child, C. M. "Psychological Foundations of Animal Behaviour," 1922, ch. 16 and 17.

[3] Clark, L. Pierce. "Nature and Pathogenesis of Epilepsy," *New York Med. Journ.*, 1915.

[4] *Idem.* "A Further Study of Mental Content in Epilepsy," *Psychol. Bull.*, 1917.

[5] *Idem.* "Clinical Studies in Epilepsy," 1917, p. 37.

[6] Herrick, C. J. "Determinism and Freedom; a Biological View."

[7] Kantor, J. R. "The Nervous System: Psychological Factor or Fiction," *Journ. of Philosoph.*, 1922, **19**, 38-49.

[8] Lille, R. S. "The Place of Life in Nature," *Journ. of Philosoph. Psychol.*, Sci. Methods, 1920, **17**, 477-493.

Notices of Recent Publications.

Brains of Rats and Men. By C. Judson Herrick. Pp. 382, with 53 illustrations. Chicago: University of Chicago Press. London: Cambridge University Press. 1926. Price 15s.

Professor Herrick is already well known to English readers as a brilliant comparative anatomist, and especially as the author of "An Introduction to Neurology," in which the basic principles of the development and elementary functions of the nervous system are so clearly presented. Within the last few years a good deal of his work has been devoted to psychology, to which he has made some valuable contributions.

The volume now under review originated in a course of lectures recently delivered on "Mechanisms of Control of Animal Behaviour." This title would perhaps indicate its subject better than any other. Rats and men are the two mammals whose behaviour has been most intensively studied, and, as one lies low in the mammalian scale and the other at its apex, they have been selected for a study in the contrast of stages of cerebral development and function. The first half of the book is devoted to a review of the phylogenetic growth of the brain and the functions in different stages of development of its constituent parts. Here the main essentials of comparative nervous anatomy and physiology are discussed briefly, but so lucidly that even the student with no previous knowledge cannot fail to understand the main principles, at least, of their development. The chapters on "The Origins of the Cerebral Cortex," "Cerebral Cortex and Corpus Striatum," and "The Corpus Striatum of Mammals," may be cited as particularly interesting reviews of functional development correlated with structural growth.

The second part of the book contains chapters on "How do Rats Learn?" "Mechanisms of Learning in the Rat," and "Localization of the Learning Process in the Cerebral Cortex of the Rat," as well as chapters on the frontal lobes and the association centres. These are largely based on Lashley's experimental observations, and are the more valuable as Herrick subjects Lashley's conclusions, some of which he cannot accept, to a critical analysis.

The final chapters on "Consciousness," "The Subconscious," "Vital Reserves," and "The Sources and Ends of Human Effort," are more frankly psychological; but the subject is treated by one of the few capable of doing so from the biological side and with biological technique. His claim that "we have integrated our living—all of it—as biological processes" indicates the author's plan.

Some of his conclusions will certainly be criticized by psychologists of

various schools, but all must admit that Herrick, in his attempt to treat mind as a phenomenon of organic life, has made a valuable contribution to placing psychology on a scientific basis.

Handbuch der Neurologie des Ohres. Herausgegeben von G. ALEXANDER, O. MARBURG und H. BRUNNER. III. Band. S. 825, mit 200 Abbildungen. Berlin und Wien: Urban und Schwarzenberg. 1926. Price 60 M.

The two parts of the first volume of this valuable and comprehensive treatise on the neurology of the ear have been already reviewed in this Journal. The second volume has not yet appeared. The third volume opens with a long chapter by Marburg on tumours involving the cochlear and vestibular systems and the cerebellum, in which the effects and the special symptoms of neoplasms in the cerebello-pontine angle, the cerebellum, the fourth ventricle and the brain-stem between the medulla and mid-brain, are discussed. This is not only the fullest, but one of the most scientific contributions to this subject to be found in the literature; in it the author's own experiences are judiciously controlled by the statements and conclusions of others. The text is not, however, overladen by the citation of authorities, for much of the loose writing that unfortunately confuses this subject is neglected. Marburg's chapter will, in fact, remain for long a standard contribution to the subject of tumours of the posterior fossa of the skull, and it is to be hoped that, though included in a special textbook, it will not escape the attention of physicians and neurologists. In the succeeding chapter Denk writes on the operative technique of cerebral surgery, including in it intervention on all parts of the brain. This is one of the few chapters in which English work has been too obviously neglected.

Sgalitzer contributes a short chapter on the treatment by X-rays of affections of the ear and of cerebral tumours. In the next section, which is titled "Dyskinesias and Dystonias," Pollak deals with the question of tonus with special reference to the influence of the labyrinth on it. The various manifestations of disturbance of tonus in man by affections of the cerebellar and extrapyramidal systems are also carefully described; the treatment of the subject is, in fact, so comprehensive that it includes progressive lenticular degeneration, chorea, torticollis, &c. In a chapter on the neuroses and psychoses, Leidler and Loewy write on the part played in them by affections of cochlea and labyrinth. Raimann deals with epilepsy and the traumatic neuroses, Urbantschitsch with the otogenic reflex neuroses, Stransky with aural affections in the psychoses, and Ohm with miner's nystagmus. There are also sections on sea-sickness, the relations of the labyrinth to the vegetative system, spasmus nutans, and on the nervous and labyrinthine symptoms that develop in airmen. Alexander contributes an article on the nervous disturbances of the ear in cretinism, myxœdema, and other endocrine affections, and Bauer and Stein complete the volume by a short chapter on the blood diseases and the auditory organs.

This volume is as carefully edited and printed as in the preceding parts, and the illustrations are again excellently reproduced. The editors must be congratulated on the completion of a monumental task, and in the publication of volumes that must claim a place in the libraries of all neurologists, as well as in those of otologists.

Ueber die Agraphie und ihre Lokaldiagnostischen Beziehungen. Von G. BERMAN und O. PÖTAL. S. 380. Berlin: S. Karger. 1926. Price 24 M.

The authors had the opportunity of studying carefully an ambidextrous man with a circumscribed gliomatous tumour of the right parieto-occipital region, which was later successfully removed. A more or less pure agraphia was the first local symptom observed, and the last to disappear during recovery. The greater part of their large monograph is devoted to a description and an analysis of the agraphia presented by this case and of its relation to other symptoms, as apraxia and alexia, which developed during the course of the illness. There is also a long discussion on the nature of the special function of the central graphic region, which they place in the parieto-occipital gyri, and of its relations to the other central mechanisms of speech. The localization of the lesions in many verified cases is also described and correlated with the authors' personal observations. The remaining third of the monograph contains critical summaries of other types of disturbance of writing, and discuscians of the theories of agraphia which have been propounded by others. The book is a valuable contribution to the study of the mechanism of speech.

Zur Bewertung der chirurgischen Behandlung der Spina Bifida. Von KARL M. STOCKMEYER. S. 46. Berlin: Karger. 1926. Price 2.20M.

In order to determine the value of operative procedures on various forms of spina bifida, Stockmeyer has collected and analysed the histories of forty-two cases which had been treated in the Bâle children's hospital, and the records of 171 additional cases from the literature; 129 of these cases had been operated upon, with the result that about 40 per cent. were cured and 15 per cent. improved. This compilation is, therefore, valuable in that it will direct attention to the fact that surgical treatment offers a greater chance of success than is usually believed. It also contains many interesting details that are worthy of study by the surgeon and the children's specialist, as well as the neurologist.

Vagotonies, Sympathicotonies, Neurotonies. Par A. C. GUILLAUME. Pp. 281. Paris: Masson et Cie. Price 14 fr.

This little volume attempts, as its subtitle indicates, a description of the clinical effects of unbalanced conditions of the sympathetic and parasympathetic nervous systems.

The author, accepting the conception of vagotony of Eppinger and Hess, proceeds to describe the physiological effects of stimulation of vagus and sympathetic, and the tests which may be used clinically to determine their activity. When he tries to apply these ideas to cases, however, the classification into vagotonics and sympathicotonics breaks down, and most neurasthenic patients are found to present features of both, a condition the author calls "neurotonic," or "dystonic."

The book is brightly and clearly written, and has a good bibliography of the older literature as well as the recent work on the subject, in French, English, German, and Italian. There is a full table of contents, but, as with most French books, no index.

Epilepsy. Von L. J. J. MUSKENS. S. 395, mit 52 Abbildungen. Berlin: J. Springer. 1926. Price 30 M.

This is a difficult book to review or appraise. Its subtitle, "Comparative Pathogenesis, Symptoms and Treatments," indicates that one of the author's objects in undertaking the experimental researches which are really the basis of his monograph, was to solve the riddle of the pathogenesis of epilepsy. Though it cannot be pretended that he has succeeded in this, there is no doubt that his investigations have brought many interesting facts to light; their exact bearing on epilepsy may be, however, a matter of dispute. It has been for long known that the injection of certain drugs, as camphor monobromate, santonin, absinthe and others, raises the reflex excitability to cutaneous and acoustic stimuli, with the result that local or generalized myoclonic twitchings result. These twitchings, which resemble epileptic myoclonus, are taken as a possible key to the investigation of experimental epilepsy. Muskens regards these myoclonic spasms as a special reflex, or rather "after discharge," and nearly half his book is devoted to what he calls the myoclonic reflex. He has shown that this reflex is to some extent dependent on the integrity of the pyramidal tract, and that it may be also influenced by lesions of von Monakow's bundle and of the formatio reticularis. But reflex centres for the myoclonic reflex are also identified in the pons and medulla, and the reflex can be elicited even from an isolated spinal cord. The direct applications of his experimental results to the pathological or clinical study of epilepsy consequently seem unsatisfactory and forced.

The later sections, which deal with the various manifestations of epilepsy in man, are less open to criticism. Here the author's extensive experience and his thorough knowledge of the literature of the disease are evident, and though there can necessarily be little new in the presentation of a subject that has been so frequently and exhaustively written on from the clinical side, many physicians will welcome the opportunity of studying his methods and conclusions. Perhaps the most interesting chapters are those on the psychical disturbances associated with or following seizures, and on traumatic and focal epilepsy. Only a few pages unfortunately are given to the pathological anatomy

of the disease, a matter to which a good deal of instructive discussion could have been devoted.

Epilepsy: A Functional Mental Illness. By R. G. Rows and W. E. Bond. Pp. 138. London: Lewis and Co. 1926.

As Rows died before the book was completed for the printer the responsibility of its publication has fallen on Dr. Bond, who has, however, not felt justified in making any material changes in the original manuscript, though he admits that if his collaborator had survived much might have been altered. The book, which is based on the author's experiences while treating psychoneuroses in a Ministry of Pensions Hospital, disregards much of the recent work on epilepsy, and deals with this disease only as a form of mental illness which is amenable to treatment by psychotherapeutic methods. Their treatment is divided into three stages: first "explanation," or exposing to the patient the physiological processes which they assume precede or are concerned in the attack; secondly, "exploration," or the establishing of chains of associated ideas and memories, and finally, "re-education" to eradicate the habits of faulty reaction. The first impression of any reader will be failure of the authors to distinguish between true epilepsy and convulsive seizures of other nature, in fact, some of the cases referred to were most probably not epileptic at all. It is also regrettable that sufficiently complete case histories are not provided, to enable one to see the nature of the material on which their conclusions are based.

Mind and its Disorders. By W. H. B. Stoddart. Pp. 593. Fifth Edition. London: Lewis and Co. 1926. Price 21s.

The appearance of five editions within the last eighteen years is an indication of the usefulness and popularity of Stoddart's textbook on "Psychiatry." The present edition is little altered from the preceding one, but the treatment of general paralysis by malarial infection and by tryparsamide are now included. A chapter on "Encephalitis Lethargica" has been added, but it can scarcely be claimed that the multifarious mental changes that accompany its onset, or follow later, are adequately described or discussed. The book will undoubtedly maintain its reputation as one of the most useful on the subject in the English language.

The Mind in Disease. By M. P. Leahy. Pp. 178. London: Heinemann. 1926. Price 6s.

This little book consists largely of the histories of patients who were relieved or cured by suggestion, which seems to be the only method of psychotherapy employed by the author; many of its pages in fact are devoted to the recital of his own cure from pain, depression, constipation, insomnia, various phobias and self-consciousness. A long list of conditions, in the treatment of which he has been successful, is appended; it includes all sorts of

disorders, as baldness, dyspnœa, epileptiform fits, "literary paralysis," and pain due to different organic causes.

There is rarely evidence of an attempt to analyse or determine the causes of these disorders, and but little psychological insight into their nature is shown.

A Descriptive Atlas of Visceral Radiograms. By A. P. BERTWISTLE and E. W. H. SHENTON. Pp. 250, 327 figures. London: Henry Kimpton. Price 21s. net.

This is a collection of radiograms illustrating normal and diseased conditions of the viscera and soft tissues, and forms a companion volume to an "Atlas of Radiographs of Bones and Joints" compiled by one of the authors. The reproduction of the X-ray photographs is well done. Naturally over one-third of the radiograms deal with the alimentary tract; the urinary tract and respiratory systems are also well illustrated.

In the section dealing with the nervous system there is a description of an original method for localization in the brain. The base-line used is a horizontal one running from the glabella to the external occipital protuberance, and measurements are made from the centre of this line, and not from its anterior or posterior end. Thus in a lateral view the point from which measurements are made is central, and covers the most important areas on the brain surface. Anteriorly and posteriorly there must be much distortion owing to curvature. The method seems to be founded on good principles, but a large number of cases verified by operation or autopsy is required before it can be accepted. The difficulty, as in all X-ray work, is to show all that is there; mere negative evidence is of no value.

The X-ray illustrations of the book are so well reproduced that it is a pity the editing of the text has allowed numerous misprints and slips of expression to appear. For example, lipiodol always appears as "lipoidal."

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd, St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.